JUNE 1960
VOL. XXI NO. 6

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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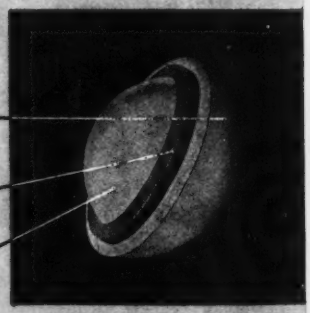

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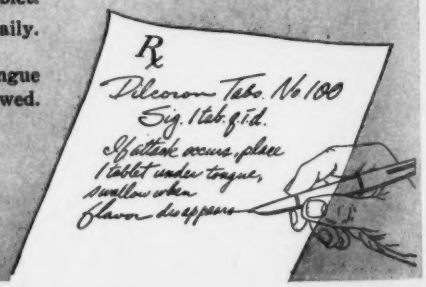

Winthrop LABORATORIES
NEW YORK 18, N. Y.

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Editorial

The Recognition of Angina Pectoris

IN 1772 William Heberden's classic description of angina pectoris was first published. Heberden, one of England's outstanding physicians, was also a scholar who possessed "the art of clear and accurate description, so that his vivid portrayal of the symptoms of angina pectoris, recorded in remarkable clarity, stand unchallenged today and is without a doubt one of the most cherished and brilliant masterpieces of the past."[1]

The following is a verbatim quotation from Heberden's *Commentaries on the History and Care of Diseases* as published posthumously in London in 1802 by one of his sons.[1]

But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris.

They who are afflicted with it, are seized while they are walking, (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have past their fiftieth year.

After it has continued a year or more, it will not cease so instantaneously upon standing still; and it will come on not only when the persons are walking, but when they are lying down, especially if they lie on the left side, and oblige them to rise up out of their beds. In some inveterate cases it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool, or speaking, or any disturbance of mind.

Such is the most usual appearance of this disease; but some varieties may be met with. Some have been seized while they were standing still, or sitting, also upon first waking out of sleep; and the pain sometimes reaches to the right arm, as well as to the left, and even down to the hands, but this is uncommon: in a very few instances the arm has at the same time been numbed and swelled.

It is of some interest that among Heberden's friends and colleagues were the brothers John and William Hunter, both physicians of note. The former, a celebrated surgeon, had angina pectoris and contributed to the knowledge of this entity by keeping personal records of his own illness. Apparently he suffered many severe attacks of angina, and his observations and descriptions of the symptoms and signs of the disorder were the first recorded by a physician suffering from this disease. As so frequently quoted he said that his "life was in the hands of any rascal who chose to annoy and tease him." It was generally agreed that "the violent disagreements he had with his colleagues at St. George's Hospital hastened his death, which occurred on October 16, 1793, following a meeting of the board of governors

of the hospital, at which a colleague had directed some disparaging remarks to him."[1] According to Willius[1] the postmortem examination of Hunter furnished one of the early accounts demonstrating the coexistence of angina pectoris and coronary sclerosis.

Let us now turn to a more recent description of angina pectoris as published in 1953 in the *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*.[2] We find the following remarks about the "anginal syndrome," more commonly known as angina pectoris:

> In this syndrome the major symptom is thoracic pain, which is precipitated usually by effort but sometimes by excitement, a heavy meal or exposure to cold. The pain is usually substernal or just to the left of the sternum. Occasionally the pain is epigastric and in rare instances it may be localized in the neck or the left arm or shoulder.
>
> There is a tendency for the pain to radiate, most frequently to the left shoulder and arm and occasionally to the fingers. Less frequently it may radiate to the neck, jaw and teeth, to the back, upper abdomen, or to the right shoulder and arm. At times the pain will start at one of these points before focusing on the anterior surface of the chest.
>
> The intensity varies from a slight sense of heaviness to a severe crushing pain. Since the precipitating cause is commonly physical exertion, rest usually causes the pain to subside. The length of the episode, therefore, is relatively short. Occasionally an attack may come on while the patient is at rest or even when asleep.
>
> The pain is often accompanied by a sense of choking or inability to breathe which is also relieved by rest. The patient will often complain of flatulence as well. If the attack is not relieved by rest or a nitrite and lasts for an hour or more, and especially if it is accompanied by circulatory collapse, myocardial infarction should be strongly suspected. Occasionally the pain of myocardial infarction may be identical with the pain of the anginal syndrome. The associated symptomatology and the subsequent course will determine the diagnosis.

It seems quite obvious after reviewing these quotations written about 200 years apart that the clinical features of angina pectoris as first described by Heberden are essentially the same as those mentioned in the "Criteria." In other words there has been general agreement for many years as to the nature of this symptom-complex. There is still considerable difference of opinion, however, as to the mechanism that initiates the syndrome. It is thought by many that angina pectoris represents an abnormal physiologic, and possibly chemical, mechanism rather than a disease entity. It therefore is not interpreted by them as being synonymous with coronary arteriosclerosis. The underlying disturbance is probably one of anoxia of the myocardium caused by transient inadequate blood flow to the heart muscle fibers. Needless to say other explanations are also entertained.

As based on the clinical and pathologic findings in many cases of angina pectoris, the majority of patients with this disorder have some underlying cardiac ailment, most often disease of the coronary arteries. It also occurs, however, in patients with syphilitic aortitis complicated by aortic insufficiency or by coronary ostial stenosis, as well as in patients with rheumatic heart disease, especially in the presence of aortic valvular deformities, i.e., stenosis or insufficiency. Congenital anomalies such as patent ductus arteriosus may occasionally be associated with angina pectoris. It is also known to occur in hyperthyroidism, anemia, and in a variety of other disorders, some of organic nature, others of functional origin.

The recognition of angina pectoris is dependent primarily on the correct interpretation of a patient's symptomatology. The latter in turn is obtained by a careful and detailed history, taken not by a nurse or secretary, but by the examining physician. Physical signs may be completely normal, including normal heart size, normal heart sounds, a normal sinus rhythm, and normal blood pressure determinations. White[3] stated that in about one fourth of all cases of angina pectoris examination fails to reveal abnormality of the heart. *Of most importance and frequently overlooked is the fact that a 12-lead electrocardiogram may be normal.* This is so in a high proportion, some 20 to 30 per cent, of patients with angina pectoris. In a series of over 400 patients with angina pectoris due to coronary sclerosis, electrocardiograms were normal in some 28 per cent.[4] Mainly because of this fact many physicians are misled and therefore in con-

sequence many patients with angina pectoris are given erroneous negative diagnoses. Some of these patients are informed that they are in normal health or that they are neurotic or are given a variety of other explanations for their complaints.

The failure of some physicians to obtain a thorough history in patients with angina pectoris is of great concern. They seem to rely mainly on electrocardiographic data recorded after exercise tests of varying degrees of exertion in order to determine whether or not a patient has the anginal syndrome. Occasionally myocardial infarction is precipitated by exercise electrocardiogram tests, although the number of such reports in the literature is small.[5, 6] This may be due to a natural reluctance to report a deleterious effect following a test of any kind. There are also known instances of fatal attacks of myocardial infarction that developed during or immediately after exercise in patients who were known to have had angina pectoris but were nevertheless submitted to such a test.[7] Patients with so-called atypical angina pectoris and known to have normal resting electrocardiograms have developed signs of myocardial injury including infarction in the electrocardiogram following an exercise test. This has occurred even in instances in which the exercise was discontinued promptly after the patient experienced chest pain. The author recently saw 2 such cases in consultation.

Master,[8] whose exercise tests are employed very frequently, has never had an accident during the performance of many thousands of "two-step" exercise tests. He has stated that accidents following tests have been reported in the literature but that "in these cases either the test undertaken was not the Master test, or it was contraindicated because the resting electrocardiogram was abnormal and/or the patient was obviously sick." He states that if it is insisted that the resting electrocardiogram be normal before exertion is attempted, added assurance is thus obtained. A recent study[9] of 250 patients with definite coronary disease that included the use of the "two-step exercise test," made by Master and his associates, revealed that there were those who had a "classic anginal syndrome" as well as patients who had had a previous coronary occlusion and presented abnormal electrocardiograms indicative of previous infarction. Nevertheless, Master[9] is of the opinion that "if his simple directions are followed, no accidents will occur except possibly by sheer coincidence."

An exercise electrocardiogram test is indicated in only a few patients, since an accurate diagnosis of angina pectoris can practically always be made by means of a careful interrogation. Sometimes a patient needs to be seen on 2 or more visits if the initial history is vague or atypical for an anginal syndrome. Such a patient should be instructed to observe more closely the characteristics of his complaint and the circumstances under which it appears as well as its response to rest and to nitroglycerin. In those few instances in which, despite careful questioning, a diagnostic history cannot be obtained or if objective evidence of underlying coronary disease is essential because of insurance or medicolegal reasons, then an exercise electrocardiogram test may be of some help. An electrocardiogram taken at rest, however, should always be recorded and recognized to be within normal limits before submitting the patient to exercise.

A great variety of ailments associated with chest discomfort are not infrequently listed as closely resembling the anginal syndrome and, therefore, in need of being differentiated from it. If the distinct clinical features of angina pectoris are kept in mind, however, this need of differentiation from other conditions will rarely be indicated. In practically every instance the typical history is sufficient to distinguish the anginal syndrome from those diseases simulating it. Unfortunately, it is very time-consuming for the average practicing physician to obtain a careful clinical history.

In closing this editorial I think it most appropriate to quote the introduction to an address on *Cardiac Symptoms* presented at the 1951 meeting of the American College of

Physicians by Sir John Parkinson[10] of England.

The subject of symptomatology will always retain its importance in medicine because symptoms form the first contact between patient and doctor. It is the voice of nature, and when a patient complains he enters our world and we recognize a human need. For convenience I shall apply the term "symptoms" to subjective sensations of which the patient complains. While everyone agrees on their value in approaching a diagnosis, symptoms have been moved to the background by current interest in signs and in scientific technic. But if we apportion too little time for eliciting symptoms, we shall suffer in our diagnosis. Besides, knowledge acquired by the art of listening and of questioning has value far beyond a lead towards the diagnosis. A doctor learns what kind of human being faces him, and what reaction he is making to his malady.

These remarks, by another outstanding physician in England's great medical heritage, are a fitting counterpart to those of Heberden as quoted verbatim at the beginning of this editorial.

CLARENCE E. DE LA CHAPELLE

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Neuroses of the Heart

Angina Pectoris

In fatal cases of angina the coronary arteries are almost invariably diseased, either in their main division, or there is chronic endarteritis with great narrowing of the orifices at the root of the aorta. Experimentally, occlusion of the coronary arteries produces slowing of the heart's action, gradual dilatation, and death within a very few minutes. Cohnheim has shown that in the dog ligation of one of the large coronary branches produces within a minute a condition of arrhythmia, and within two minutes the heart ceases in diastole. These experiments, however, do not throw much light upon the etiology of angina pectoris. Extreme sclerosis of the coronary arteries is common, and a large majority of the cases present no symptoms of angina. Even in the cases of sudden death due to blocking of an artery, particularly the anterior branch of the coronary artery, there is usually no great pain either before or during the attack. The lesions of the nerves described by Lancereaux, Hadden, and others cannot yet be correlated satisfactorily with the symptoms of true angina. Various forms of true angina have been recognized, but the differences, in the majority of instances, are not sufficiently marked to permit a separation.—WILLIAM OSLER, M.D. *The Principles and Practice of Medicine.* New York, D. Appleton & Company, 1893, p. 656.

Atheroma and Thrombosis

Major Threats to Our Health Today

By PAUL D. WHITE, M.D.

I HAVE accepted the challenge of speaking to this erudite society on the subject of their chief interest because of my strong conviction that I may have something of clinical importance and interest from my own experience to add to the sum of recent knowledge already established, and possibly such experience may help in the direction of further research, clinical and basic.

Atherosclerosis and thrombosis are two different problems unless we accept the thesis that all atherosclerosis is based on previous thrombotic processes as presented by several investigators and particularly of late by Professor Duguid. Similarly, I regard hypertension as an abnormality distinct from atherosclerosis although hypertension undoubtedly is an aggravating factor and atherosclerotic obstruction of a renal artery can cause hypertension (like Goldblatt's clamp), while marked atherosclerotic lesions in older people can produce systolic hypertension by the establishment of a full pulse pressure due to inelasticity of the major arteries. My current belief is that the hazard is primarily secondary to the atherosclerosis itself, although I quite agree that superimposed thrombosis, blocking any one of a number of vessels such as the coronary, the internal carotid, the renal, or the iliac arteries can have very serious consequences. However, at least two thirds of the cases of sudden death encountered by Dr. Milton Helpern, with his long experience in the Coroner's Office in New York City, showed extensive coronary atherosclerosis with no fresh thrombosis. A minority do show thrombi. In other words, one can die of angina pectoris without an actual fresh occlusion. I shall, therefore, base my remarks today primarily on the atherosclerotic lesion and its clinical significance and have less to say about the complicating or admittedly serious thrombosis that is superimposed. Nor shall I have much to say about the hemorrhages in the coronary intima or atheromatous plaques long ago described as common by Paterson of London, Ontario, and recently confirmed by Helpern and his associates in New York.

I wish to quote at the beginning of this discourse from Shakespeare and later from Lancisi. In *As You Like It,* Act II, Scene VII, Jaques in the forest, where a table is set, speaks as follows in answer to the Duke's statement of

> Thou seest we are not all alone unhappy:
> This wide and universal theatre
> Presents more woeful pageants than the scene
> Wherein we play
> *Jaq:* All the world's a stage,
> And all the men and women merely players;
> They have their exits and their entrances;
> And one man in his time plays many parts,
> His acts being seven ages. At first the infant,
> Mewling and puking in the nurse's arms,
> Then the whining school-boy, with his satchel
> And shining morning face, creeping like snail
> Unwillingly to school. And then the lover,
> Sighing like furnace, with a woeful ballad
> Made to his mistress' eyebrow. Then a soldier,
> Full of strange oaths, and bearded like the pard,
> Jealous in honour, sudden and quick in quarrel,
> Seeking the bubble reputation
> Even in the cannon's mouth. And then the justice,
> In fair round belly with good capon lined,
> With eyes severe and beard of formal cut,
> Full of wise saws and modern instances;
> And so he plays his part. The sixth age shifts
> Into the lean and slipper'd pantaloon,
> With spectacles on nose and pouch on side,
> His youthful hose, well saved, a world too wide
> For his shrunk shank; and his big manly voice,
> Turning again toward childish treble, pipes and whistles in his sound. Last scene of all,
> That ends this strange eventful history,
> Is second childishness and mere oblivion,
> Sans teeth, sans eyes, sans taste, sans everything.

The Lyman Duff Memorial Lecture, Council on Arteriosclerosis of the American Heart Association, American Society for the Study of Arteriosclerosis, Chicago, November 8, 1959.

In Shakespeare's day, life was short. Although we know not the actual ages in years to which he assigned these 7 periods of life, we may guess that they were short in time. The expectation of life was very limited, probably not much over 20 years, and men and women were already old at 40. In fact, 250 years after Shakespeare, which would be about 100 years ago, a woman died at 45 in a ward of the Massachusetts General Hospital and the only diagnosis on the record at that time, as I have read myself, was "old age." We know now that one does not die of old age. I myself have always found some adequate cause, such as would be noted in younger people, for example, pneumonia, severe coronary atherosclerosis, cerebral vascular accident, rupture of an abdominal aortic aneurysm, and many other events of the sort. Let me guess that Shakespeare meant that an infant or young child, that is, the first age of man, might extend from birth to the age of 5, the second period that of the whining school boy from 5 to 15, the third age that of the lover from 15 to 25, the fourth that of the soldier from 25 to 35, the fifth that of the judge, that is, an experienced professional man, from 35 to 45. Quite likely the judge in his early 40's "in fair round belly with good capon lined" had a fair amount of atherosclerosis, which may not have allowed him to survive into the sixth and seventh ages. From 45 to 55 we come to the "lean and slipper'd pantaloon," and finally at 60 second childhood. This division of years is a probability, not a certainty.

Today with the great extension of life, including not only the average expectation, which is about 70 instead of 30 as in Shakespeare's time and 40± a hundred years ago, we know that many healthy people are active in the sixties, seventies, and eighties. Rarely is pneumonia any more the old man's friend although a patient of mine, aged 107½, who was quite healthy as to his heart and cerebral condition, unfortunately did die of pneumonia, which had threatened to kill him 105 years earlier when he was an infant.

I would like to paraphrase Shakespeare's 7 ages of man by setting up my own subdivisions of life, namely 5 periods of 20 years each, which I am quite sure might well be our goal perhaps within a generation and, I certainly hope, not much later. I would divide life into 5 periods of 20 years each, the first from birth to 20, that of youth. Once upon a time this was the terrible time of life, and actors on the stage in these 2 decades died of infections right and left. Even when I was a medical student and an intern in the hospital and for a few years afterwards, the infant and childhood mortality was very high. Babies, whom I helped to take care of in 1911, died like flies, chiefly of dysentery before the pasteurization of milk. Children died of diphtheria. I myself had it but fortunately was rescued by antitoxin. Smallpox still occurred. My own father almost died of smallpox in 1881 in London and he had typhoid fever 3 times during his years of family practice. I myself escaped typhoid but it was still so current that our wards were full of it every fall. There was no room for any cardiovascular patient or anybody with cancer. Meningitis, empyema, and mastoiditis were constant emergencies and the toll was frightful. Just to think back to those days is like redreaming a nightmare. The young doctors today cannot imagine what we faced. We had a good deal of malignant endocarditis, that is, subacute bacterial endocarditis, and it was 99 per cent fatal. Tuberculosis led the list in mortality. We did not have any cholera, to be sure, although my own father's mother had died of it on Bunker Hill in Charlestown in 1860 in her very early 20's, when father was still a young infant.

Henry Christian, who was our Professor of Medicine, when I was in medical school, gave his first 6 lectures in the theory and practice of medicine on typhoid fever practically verbatim from the first chapter of Osler's textbook, the idea being that if we knew this infection we knew medicine. Today the first 6 lectures might well be given on the theory that if we know atherosclerosis we know medicine, but we certainly hope that a generation from now, this too may be in large part past history, at least in youth and middle age. The challenge is here. There is no reason why, hav-

ng accomplished what we have in the control of infections, we may not accomplish still more in the control of the current hazards to health which, by the way, include automobile accidents on the road, as well as cancer and cardiovascular disease.

I try to refer nowadays to cardio*vascular* disease rather than heart disease underlining the vascular part of the word and emphasizing the fact that most of our serious heart disease is not due to primary heart muscle (myocardial) disease, but rather to vascular disease. This is just as much true of cerebral diseases, diseases of the kidney and other viscera and of the legs. These troubles in major part are due to the same process, atherosclerosis, which affects the intima in all these areas of the circulation. The chief hazard in the first age period of man today (birth to 20), as I have outlined, is, so far as I know, that of accidents, with infections way down. We have not abolished them all by any means, but we have gone a long way. Accidents on the road were almost unknown when I was a medical student. It is a ridiculous state of affairs now to allow our young people to slaughter themselves on the roads.

We come now to the second 20-year period from 20 to 40. These, I call, the critical years. It is in this period of life when all seems to be going well that atherosclerosis gets going even while the candidates for trouble look so healthy, in fact too healthy, robust, with high color, and symptomless. These are the critical years for countless numbers of men in whom this process of atherosclerosis begins to be laid down. The average man in America settles down at about 25 to a life of physical indolence although with often great nervous activity in his profession or business. He has no more time to exercise or to have relaxing recreation of any sort. He has an automobile and can hardly move without it. He has a television set before which he lolls in the evening on return from his office. And his wife cooks too well. He puts on a pound or 2 or 3 of weight every year during this period; that extra weight is not muscle. When I see him as a patient at the age of 45 to 50, he is 20 to 30 pounds heavier than he was at 25. I always inquire now of my patients with coronary heart disease at the average age of 50 what their weight was at 25. It is almost invariably true that much weight has been added slowly through the years, though sometimes rapidly during the earlier years soon after marriage. Of course, it is not the actual fat under the skin to carry around that is important. This probably does not increase the burden on the heart much although it may be uncomfortable when stooping. In fact it might be good exercise to carry this weight around if there were not an infiltration into the arterial intima of much of the fat. A few ounces in the wrong places must be very much more harmful than many pounds tucked away under the skin here and there throughout the body. During these decades from 20 to 40 there are still infections to guard against, but we no longer have so much the threat of syphilis or recurrence of rheumatic fever from a streptococcus sore throat, or even appendicitis. Hypertension may start during these 2 decades, perhaps associated with the way of life and quite likely also on a hereditary basis, which is incidentally back of much of our early atherosclerosis.

Then we come to the third age of man from 40 to 60, which is the middle period of middle life where much of the disease that has been slowly building up becomes apparent by symptoms, signs, or sudden death. Hypertension, coronary atherosclerosis of high degree giving rise to angina pectoris, sudden death, or heart attacks with myocardial infarction, little strokes and big ones too, abnormalities of the circulation to the legs, and cancer are the chief threats through this period of 20 years. Here is the ripening of the hazard that started in the 20's or 30's. It is quite certain that the health in this period in middle age from 40 to 60 is largely dependent on what has happened before, much less in childhood, that is, before 20, than in the period from 20 to 40. It is quite obvious that we must start a campaign for "middle-aged fitness." Most of our efforts have been directed to our youth, and quite rightly, and what has been done for them has been very important. I myself belong

to the President's Council for Youth Fitness, but this is only a beginning. Much more important is now a campaign for *middle-aged fitness,* and I would like to promote this for the sake of improvement in fitness in middle age by the application of the measures about which we know a good deal already although we have not as yet all the answers.

The last 2 periods of life will also be vastly improved by this program and the male will at last have a chance to begin to catch up with the female in expected longevity. At the present time the American male expects to live only to 67 years or a bit more and the female to 73+. This difference of 6 years has increased in the last generation, largely due to the earlier hazards in middle age, chiefly atherosclerosis, which affects the male so far as the coronary arteries are concerned 24 times more often than the female under the age of 40, about 5 times more in the 40's, and about twice more in the 50's. We must make every effort to change the present inequality of these ages and the great surplus of widows over widowers in the middle of the later period of middle age, which I would put from 60 to 80.

Finally, we come to old age from 80 to 100, which can be much healthier if we can forestall some of the progressive changes in the intima of the coronary and other vital arteries earlier in life and if we can avoid hypertension and some of the other ills, including cancer of course, that strike middle-aged people. In addition to the prolongation of life we have the problem of maintaining health, that is, of adding life to years as well as years to life. It is in general true that the longer we can keep people living the more useful they can be. It is absurd to require retirement in the 60's. Most people, especially in the future, will still be very useful in the 70's and well enough to carry on quite vigorously both mentally and physically. There is no reason why a man of 70 to 80 should not continue to shovel snow if he is well, perhaps at not quite so fast a tempo. We might aim for 100 per cent mortality from coronary atherosclerosis if it kills quickly at the age of 100 during the night while the victim is asleep without any illness or incapacity prior to that time. This would mean the cancellation of the serious infections, of cancer, of accidents, of war, and many other ills. It will be a fine and perchance a final goal.

Now let me quote from a translation of Lancisi's preface and a bit of his second volume on *De Subitaneis Mortibus,* that is, on sudden death, a remarkably interesting forecast of what we see and think today.

At Rome, in the summer, autumn and winter of 1705 down to the spring equinox of 1706, were many sudden deaths. The populace as they do in a Panic, invented a number of explanations: the poor quality of the tobacco; exhalations from the earth after recent earthquakes; inferior chocolate, a mysterious poison (virus) in the air. Pope Clement XI turned, as he ought, to spiritual remedies and a special liturgy, but uniting prudence and piety, appointed in January, 1706 a committee of investigation and ordered the head physician of the Medical College at Rome to have some of the bodies dissected. Lancisi was appointed head of the Commission to report to His Holiness; Cardinal Pallavicini, the Governor of Rome, gave all possible assistance and the experiments were made in a public theatre. By means of such dissections and other observations which Lancisi now publishes he arrived at certain conclusions. Meanwhile others have published dissertations in Italian and Latin, meritorious as far as they go, but these men lacked my opportunities. First, I shall deal with sudden deaths in general, a subject of late neglected, and in my second volume shall discuss whether this disease was of a universal or a particular, or, as I believe, a mixed type. I shall add some anatomic discussion. May the Reader enjoy it.

So wrote Lancisi* in the preface of his book *De Subitaneis Mortibus* in the year 1707, 252 years ago. He continued discussing possible causes of sudden death along this same vein in Chapter 1 of Book II:

Was the cause simple (not complicated) and universal, or particular and mixed? First, was the cause particular in individual cases? We know that in certain years or seasons, death comes to men, yes and to animals such as cattle and goats, from a pestilential condition of the air or a taint in air or water, or from a scarcity or defect in their pasture, and that it rages without warning. So sang Fracastoro in his golden verses:

*Translation by Wilmer Cave Wright (unpublished —in manuscript—kindness of New York Academy of Medicine).

Sometimes tis only beasts that are chastised,
Many or only some thereof, I do remember
One summer's baleful heat; an autumn followed
With soaking rain; the south wind blew
continually,
Then every kind of goat, but of all living things
The goats alone, did perish.

But I consider it more likely that the cause of the sudden deaths at Rome was not single and absolutely common to all, but that in the majority of cases there was a special cause for each case. I conclude this from the external symptoms, and my conviction was only strengthened by experiments. For it will be shown in the following pages that the peculiar and principal cause of premature death in each case was the presence of certain seeds, which were produced gradually and were finally called into action on a sudden; as Hippocrates says: 'Diseases do not come to men suddenly but are collected and pile up little by little.' No need to blame the tobacco; since some whose nostrils were never defiled by that dust died suddenly. Or exhalations from earthquakes, since many who escaped death lived where there had been most earthquakes. Nor was the chocolate to blame, for men like Dr. Placentius, an octogenarian, or myself, accustomed to drink it as much as twice a day for 30 years either escaped altogether or had only light symptoms. On the other hand, many who never tasted it died suddenly. Nor was it a case of undetected poison in the air, for when like augurs we inspected the entrails, we found clear and well known causes for the disease.

Before the Pope ordered us to dissect, there was evidence for the theory that the cause of death was particular and not universal; in some cases there were symptoms of rupture of the blood carrying canal which had been weakened by a varix or an aneurism in the chest or abdomen. Many died of violent apoplexy due to stoppage or effusion of blood in the brain; others of a violent spasm of the heart or paralysis or obstruction of the passages of the heart and of the large arteries. Thus was hindered the passage of the blood from the heart into the lungs and the brain, and so the vital and reciprocal communication of those organs was suddenly cut off. But I must repeat again and again, that so far as I know, every one of those who died suddenly had long suffered from some disease of the fluids, the intestines, or at least of the blood vessels. . . . Therefore, to the best of my belief, these sudden deaths did not come to the healthy, but nearly always to those who had long suffered from poor health. For them this was a sort of foaming over of human nature, or an unfavorable crisis arose, with men who had long been either openly or secretly in poor health.

These remarkable observations of Lancisi were unfortunately never followed up, otherwise much more interest would have been developed in the evolution of the processes of disease that lead to sudden death, including in particular atherosclerosis, which must have been seen although it was not well described either grossly or with the help of the primitive microscopes of the day except in 1 case report in the second edition of Bonet's Sepulchretum in 1700. It is quite obvious from our experience of late years, as well as occasional notations by the more astute observers like Lancisi, that neither sudden death, nor angina pectoris, nor coronary thrombosis comes suddenly to a healthy man. The evolution of the process is a slow one, taking years at least and perhaps decades before symptoms or signs develop.

Can we, as seems quite possible, by the newer technics of angiocardiography and other simpler methods, diagnose serious degrees of atherosclerosis at a much earlier stage than we are now able to identify them? Even if we should do so, much more would have to be done before corrective curative measures might be applied. Therefore, it seems obvious to me, and I am sure to all of you, that our chief effort in research, basic and clinical, must be directed to a more intensive study of the initial processes, physical, chemical, and hereditary in order to learn how we may counteract them. Our task is 2-fold: that of the identification of the candidate for serious trouble early in life or in middle age with a study not only of the family history but also of characteristics which we have believed to be of some importance such as body build and blood chemical findings like hyperglycemia and hypercholesteremia. Although we should attempt to make some effort to protect the whole population, nevertheless the candidates are the ones we should concentrate on first. Such candidates should be identified if possible in their early years, even perhaps in their teens, at any rate not later than their 20's. For such candidates and perhaps for all of us, simple measures may be advisable even now before we have all the proof, such measures as the avoidance of any gain in weight after

the age of 25, the reduction of the animal fat content of our very rich American diet, and the institution of programs of regular exercise and relaxation of other sort too, with an effort to neutralize at least somewhat the emotional stress that is so characteristic of current urban life.

If we can also discover in the course of our researches, which is quite possible, magical remedies in the form of chemical substances to counteract hypercholesteremia and inherited enzyme defects, we may not need to carry out so much the other protective measures even though they seem very reasonable to us now. And while we are busy with our researches on these problems, we should try to correct the erroneous opinions and practices of countless individuals in this country who are still inclined to blame hard work as the primary cause of atherosclerosis and its complications.

Just one word about hard work. It is true that one can get very tired both physically and mentally from hard work, but I have yet to find a man or woman, otherwise healthy, who has, from hard work alone, become ill provided he or she carried out a sensible program of life avoiding the hazards that I have just mentioned.

In conclusion, may I express optimism about the future results of our researches, physical, chemical, hereditary, pathologic, and clinical on atherosclerosis, especially of the premature varieties. Within another generation, in fact I believe within a decade, with the present increasing tempo of vigorous research, we should have some definitive answers that will allow us to protect our men and to extend increasingly the expectation of a long and healthy life.

Again as I have frequently done in the past, I would like to end with another quotation from Shakespeare—*"Our remedies oft in ourselves do lie, which we ascribe to Heaven."*

Summario in Interlingua

Iste documento es le conferentia memorial Lyman Duff, presentate in 1959 a Chicago ante un reunion del Societate American pro le Studio de Arteriosclerosis. Le autor discute le thema de atheroma e thrombosis super le base de su conviction que in le composito "cardiovascular" il es le secunde parte que merita nostre prime attention. Iste attitude resulta del conviction que in le majoritate del casos de cardiopathia le morbo primari es non del toto myocardial sed plus tosto vascular e que, in plus, il es frequentemente un disordine vascular que debe esser incriminate primarimento quando un patiente manifesta symptomas renal o alteremente visceral.

Medical Eponyms

By ROBERT W. BUCK, M.D.

In order that people may be happy in their work, these three things are needed: They must be fit for it: They must not do too much of it: And they must have a sense of success in it.—RUSKIN. (Submitted by H. M. Marvin, M.D.)

Differential Diagnosis of the Taussig-Bing Heart from Complete Transposition of the Great Vessels with a Posteriorly Overriding Pulmonary Artery

By ALOIS BEUREN, M.D.

ACCORDING to a recent review article,[1] there seems to be some disagreement about what constitutes a transposition of the Taussig-Bing variety, what the criteria for its diagnosis are, and with what certainty this diagnosis can be made during life. There is, however, general agreement that in the cyanotic group of congenital heart disease, the various forms of transpositions of the great vessels constitute a well-defined entity as far as their physiology is concerned. The hemodynamics are characterized by the separation of the 2 circulations and the amount of blood-mixing that is allowed between them by the number and size of the additional lesions. In regard to the anatomic arrangement which may be found in transpositions of the great vessels, it is well known that the degree of displacement of the aorta and pulmonary artery and their relation to each other may vary considerably from case to case. This was early recognized by Peacock,[2] Rokitansky,[3] Lochte,[4] Spitzer,[5] and Pernkopf[6] and was clinically analyzed by Taussig.[7] Among these various forms of transpositions, the Taussig-Bing transposition is a well-described clinical and anatomic entity. Physiologically, however, the Taussig-Bing transposition is not so fundamentally different from the other types of transpositions as it is anatomically. This is notably true of the other group of transpositions with an overriding pulmonary artery and also of the complete transpositions with large ventricular septal defects. This physiologic similarity may account for the difficulty in the differential diagnosis.

Although there has been no further case reported from this clinic since Taussig and Bing described their original case in 1949,[8] a number of cases were reported in the literature;[9-17] indeed there is probably no center in which identical transpositions have not been observed. This led to the opinion that the Taussig-Bing transposition is not rare. It is the purpose of this paper to review the Taussig-Bing transpositions that were diagnosed in this clinic and to describe some characteristics that could be helpful in differential diagnosis from the transposition with posteriorly placed pulmonary artery. Furthermore, comparison will be made to some cases published in the literature.

In their first report,[8] Taussig and Bing described this malformation as "complete transposition of the aorta and a levoposition of the pulmonary artery." This report described an abnormal physiologic condition associated with a definite pathologic anatomy. There is another transposition of the aorta and an overriding pulmonary artery with a very different anatomic situation. These are the 2 transpositions with which we are concerned. In the Taussig-Bing heart, "the pulmonary artery arose approximately in its normal position, the aorta was transposed; it arose entirely from the right ventricle. There was a ventricular septal defect at the base of the ventricular septum of 1.2 x 0.6 cm. The superior portion of the ventricular septum deviated to the right to such an extent that the pulmonary orifice overrode the septal defect by a few millimeters." In other words, despite the approximately normal position of the pulmonary artery, this vessel overrode the septal defect because of the deviation of the ventricular septum. This is schematically demonstrated in figure 1, which is taken from the original paper. A muscular ridge sep-

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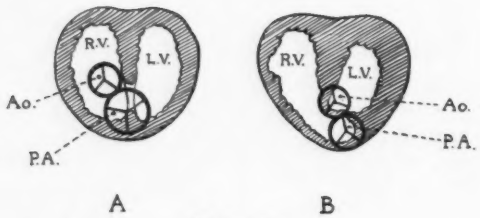

Figure 1

Copy of the original drawing in Taussig and Bing's paper. A. *The vessel position in the Taussig-Bing heart.* B. *The vessel position in the normal heart. Note that this is not the position in which the heart is placed in the body.*

arated the pulmonary artery and the aorta, so that most of the venous blood entering the right ventricle was ejected into the aorta and most of the pulmonary blood from the left ventricle entered the pulmonary artery.

In figure 1 the Taussig-Bing heart and the normal heart are not shown as they are placed in the body. In accordance with the concept of Barry and Patten,[18] and Walmsley,[19] figure 2 shows the position of the normal heart in the body; the position of the Taussig-Bing heart in the chest is shown in figure 3. These figures also show the heart as seen in the various projections on x-ray and fluoroscopy. In figure 3 it is evident that in the Taussig-Bing transposition in the anteroposterior position, the 2 vessels are side by side. In comparison with the normal position of the 2 vessels it is evident that they must lie side by side, if "the pulmonary artery occupies its approximately normal place" and the aorta is transposed in such a manner that it comes off the right ventricle.

In the second group of transposition of the great vessels in which there is a transposition of the aorta and an overriding pulmonary artery, the relation of the 2 great vessels to each other is very different (fig. 4). The pulmonary artery does not occupy its "approximate normal place," but is placed far posteriorly to the aorta. It also overrides a ventricular septal defect. The aorta arises from the right ventricle in this malformation, but directly anterior to the pulmonary artery. Thus, in the Taussig-Bing heart the aorta is transposed and the pulmonary artery overrides the ventricular septal defect in its normal place, whereas in the latter malformation both vessels are completely transposed in their relation to each other. These 2 anatomically different transpositions are frequently confused because of the similarity of the history and the possible similarity in x-ray appearance and catheterization findings.

Case Material

Since the original publication of the Taussig-Bing case in 1949, there have been 73 cases listed in the clinic file as possible Taussig-Bing transpositions. These cases were reviewed in the present study. The essential clinical features are cyanosis dating from birth, right ventricular hypertrophy in the electrocardiogram, and the characteristic cardiac contour on x-ray, namely, increased pulmonary vascularity and a very prominent pulmonary conus. The diagnosis is established if in addition to these clinical findings one or more of the following criteria are fulfilled: (1) at catheterization highest oxygen content in the pulmonary artery, systemic pressure in the pulmonary artery, and a step-up in oxygen content in the right ventricle combined with good evidence of a typical position of the pulmonary artery; (2) demonstration of the characteristic relation of the 2 great vessels to each other, either by angiocardiography or by observation of the course of the cardiac catheter during catheterization; (3) autopsy proof. If the diagnosis is based upon the catheterization findings, there should in addition be evidence of the typical position of the great vessels.

Of the 73 patients reviewed, 14 were accepted as definite Taussig-Bing transpositions (table 1). Three of these were proved at autopsy (cases 4, 8, 11). One of the autopsied cases (case 11) was clinically diagnosed without further tests. In the other 2 autopsied cases, the diagnosis was made by angiocardiography during life (cases 4 and 8). In 3 cases the diagnosis was based mainly on the catheterization data (cases 2, 12, 13), in 5 on angiocardiography (cases 1, 7, 9, 10, 14), and in 3 on angiocardiography and catheterization data (cases 3, 5, 6). Besides these 14 cases, there were 17 among the 73 cases reviewed in which the clinical diagnosis of a Taussig-Bing transposition was highly probable but in which the diagnosis was not established by autopsy, angiocardiography, or cardiac catheterization. Several of these 17 patients underwent thoracotomy for the creation of an artificial atrial septal defect. Observations of the position of the great vessels, which may be made during surgery, are not considered as diagnostic criteria in this report. In addition there

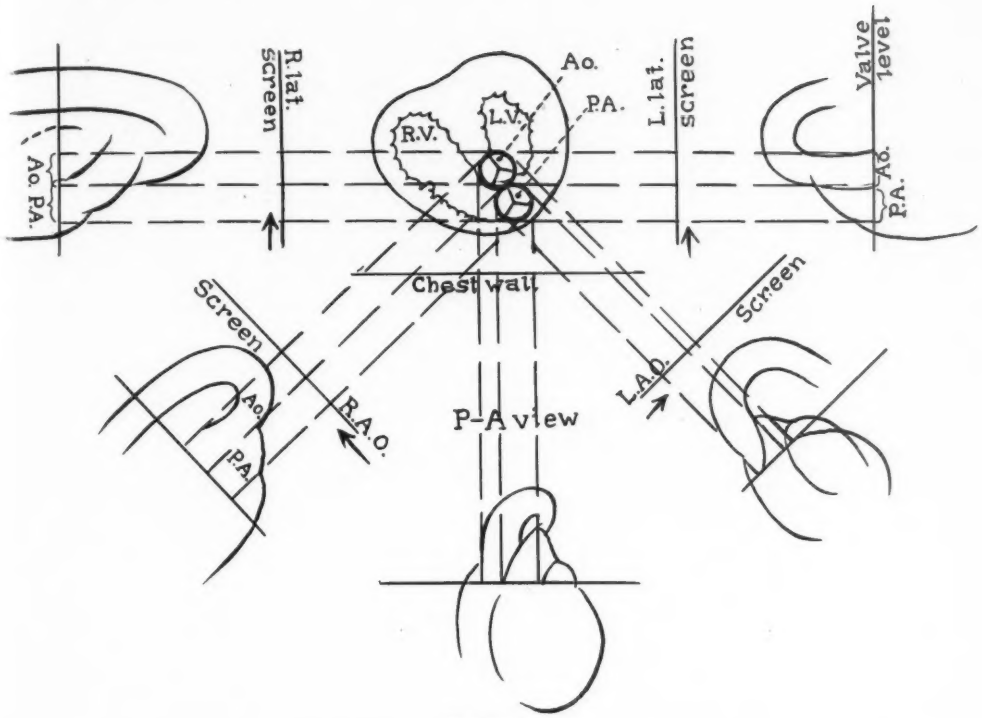

Figure 2

The normal heart as placed in the body. The lines demonstrate how the shadow of the great vessels is projected upon the x-ray screen in the different views.

was 1 autopsied case in which there was a transposition with an overriding pulmonary artery but in which no mention was made as to the exact position of the vessels. Since the specimen has been destroyed, this case cannot be classified definitively.

From the initial 73 cases, 7 were excluded because the diagnosis of complete transposition with ventricular septal defect seemed more likely, and 1 case because of the possible diagnosis of a single ventricle with a transposition. Twenty-five cases were excluded because the data were insufficient to make an absolute diagnosis. There was 1 additional case with a dextrocardia and a transposition similar to the Taussig-Bing heart. This case also has been excluded.

The history, physical, and clinical findings are similar in all 14 cases. Most of the patients were seen at yearly intervals over a period of several years. The age at the first examination ranged from 12 days to 27 years. When last seen, 6 patients were 10 years or older. There were only 3 patients above 15 and 1 patient was 27 at the time of his only examination.

All patients showed cyanosis from birth. Above the age of 1 year all had clubbing. There was only 1 patient with a history of spells of unconsciousness associated with deepened cyanosis. Growth and development were retarded, and exercise tolerance was reduced in almost all of these patients. Thirteen had a systolic murmur at the left sternal border in the third and fourth left intercostal spaces. The murmur was usually heard during the first few weeks of life. One patient had no murmur. Mid-diastolic murmurs were heard in 2 patients. Only 3 patients had a systolic thrill at the left sternal border. Ten patients had marked polycythemia. On x-ray and fluoroscopy the pulmonary vascularity was markedly increased in all 14 patients. Each had a prominent pulmonary conus similar to that of the original Taussig-Bing case (fig. 5). There was moderate to marked cardiac enlargement in all patients. Right axis deviation and right ventricular hypertrophy were present in all electrocardiograms. These findings made the diagnosis of a Taussig-Bing transposition probable. Cardiac catheteriaztion was performed in 11 patients, but the pulmonary artery was not en-

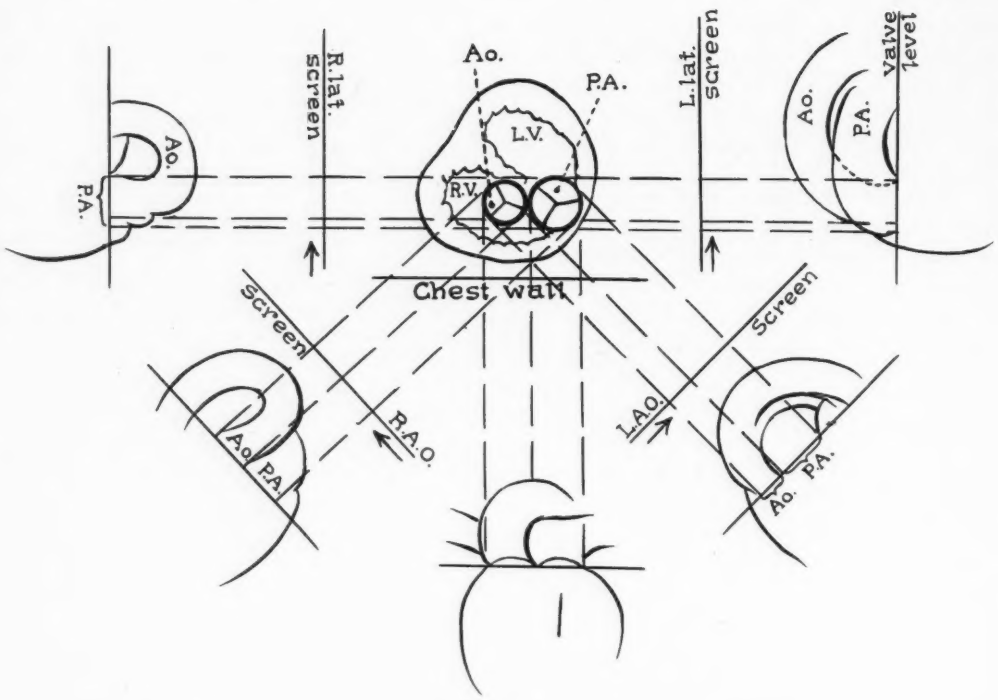

Figure 3

The Taussig-Bing heart as placed in the body. In the right anterior oblique view, appears on the screen from the right to left: chest wall, lung, pulmonary artery, aorta. In the left anterior oblique view from the left to right: chest wall, lung, aorta, pulmonary artery.

tered in 5 of them. In the remaining 6, the pulmonary artery was entered and the catheterization data provided significant information for the diagnosis of a Taussig-Bing transposition. As in the original case of Taussig and Bing, there was a large step-up in oxygen content in the right ventricle. The oxygen content in the pulmonary artery was markedly higher than in all other samples obtained. As in the original case, there was a small bidirectional shunt, and the pressures in the pulmonary artery were at systemic levels. The course and the position of the catheter were observed and this provided good evidence for the position of the great vessels. In some cases spot films with the catheter in the pulmonary artery were taken.

To obtain further information, intravenous angiocardiography was carried out in 11 of the 14 patients. This examination was unsuccessful in 1 patient. In 10 patients good evidence of the typical position of the great vessels of the Taussig-Bing transposition was obtained. The pictures were usually taken in the anteroposterior and right lateral projection. On filling of the right atrium, there is usually a good demarcation of the atrial septum. A large atrial septal defect was demonstrated in 1 patient (case 10). In each case there was a good, early visualization of the aorta immediately after the filling of the right ventricle. As first described by Taussig,[7] and later shown in angiocardiograms published by Cooley and Sloan,[20] in complete transposition there is usually an absence of the shadow cast of the pulmonary conus of the right ventricle, which shows that the pulmonary artery does not occupy its normal position. This sign was absent in all of these 10 angiocardiograms; in contrast there was a full pulmonary conus in the anteroposterior and lateral views. The right ventricular shadow in the lateral view showed the contour characteristic of a large right ventricle that is pressed against the anterior chest wall. In all of these angiocardiograms the aorta was better opacified than the pulmonary artery. This was so not only because of the origin of the aorta from the right ventricle but also because of the dilution of the contrast medium in the large dilated pulmonary artery, which receives a large amount of blood from the

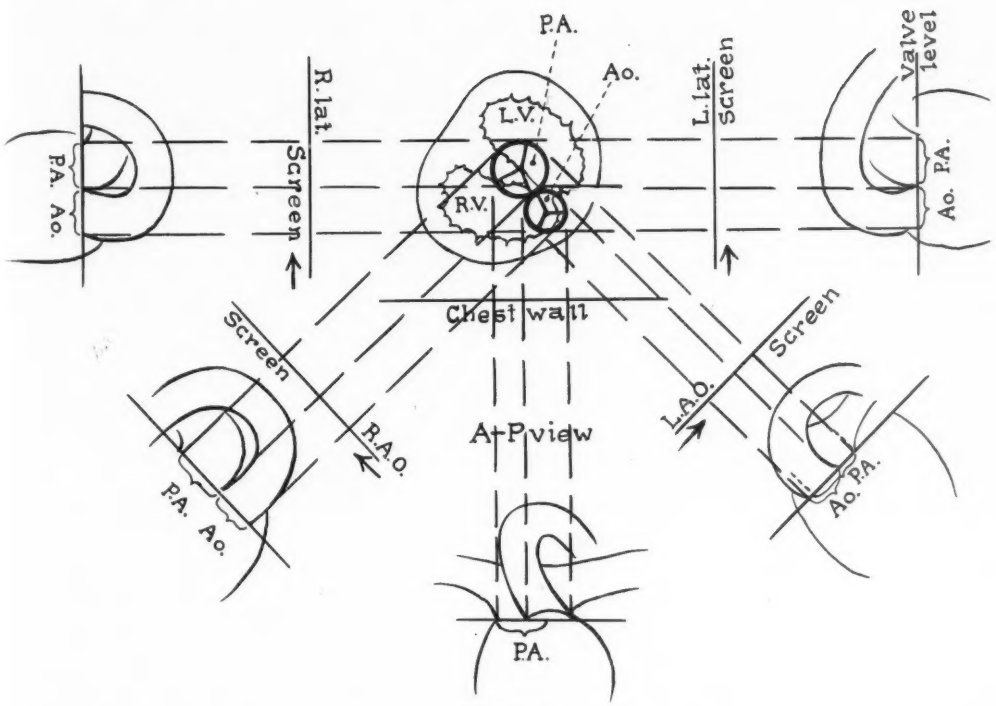

Figure 4

The transposition with posterior pulmonary artery as placed in the body. In all views the aorta is always in front of the pulmonary artery.

left ventricle. It is also possible that the muscular ridge that separates the origin of the aorta from the pulmonary artery may not allow a substantial shunt of contrast medium into the pulmonary artery. In the right lateral view the aorta was seen further anterior to its normal position, whereas in the anteroposterior projection the aorta was side by side with the pulmonary artery; (figs. 3, 6, and 7). In case 1, angiocardiograms were taken in the left anterior oblique position that showed the aorta anterior to the pulmonary artery. This is schematically demonstrated in figure 3. In the Taussig-Bing heart, the left anterior oblique view is the only position in which the aorta is projected anteriorly upon the x-ray screen.

The characteristic appearance of the great vessels as seen in all of these angiocardiograms is also demonstrated in the angiocardiogram of the original case of Taussig and Bing. The angiocardiogram was not published in the first report but is shown in figure 6. In the original case, the patient died during angiocardiography and these are the only 2 films that were obtained. There were no deaths during or immediately following angiocardiography in the present series. In 2 of the 10 patients with angiocardiographic studies, the diagnosis was confirmed at autopsy. A summary of the autopsy reports is given at the end of this paper.

From the 73 cases reviewed, it was possible to remove 4 cases in which the diagnosis of a transposition with posteriorly placed overriding pulmonary artery is considered to be established. The data of these cases are summarized in table 2. Three of these patients had angiocardiography (cases 1, 3, 4) and 1 was also studied by cardiac catheterization (case 4). In 1 case the diagnosis seems to be certain on the basis of cardiac catheterization alone (case 2). Cases 1, 3, and 4 were proved at autopsy. In 3 additional patients, the diagnosis of a posteriorly overriding pulmonary artery was made on clinical grounds alone. The distribution of the 73 cases which have been reviewed is shown in table 3. The age of the 4 patients with the diagnosis of an overriding posteriorly placed pulmonary artery ranged from 3 months to 6 years. In all of them cyanosis was present since birth, and in all but 1 a cardiac murmur was heard at birth or shortly thereafter.

Table 1

Clinical Data of Fourteen Cases of Taussig-Bing Transposition

Case no., initials, sex	Age first ex. Age last ex.	Cyanosis, clubbing, spells	Murmur, thrill	Blood count	X-ray	Angiocardiogram	Catheterization	Autopsy	Comment
(1) A-61459 P.M. Female	2 yr., 1948 12½ yr., 1958	Since birth 3 plus 2 plus No	Loud systolic, LSB Yes	RBC 8.4 Hb. 22 Het. 72	Prominent pul. conus, increased pul. vascularity	Simultaneous filling of aorta and pul. artery. Aorta anterior in LAO. Both vessels side by side	Pul. artery not entered	No	1954 artificial ASD. Vessel position at operation thought to be typical
(2) A-45637 N.H. Female	4 yr., 1946 15½ yr., 1958	Since birth 3 plus 2 plus No	Systolic apex, Slight	RBC 7.5 Hb. 21 Het. 71.3	Very prominent pul. conus, increased pul. vascularity	No	Pre and postop cath. Aorta and pul. artery entered. Ao=O_2 cont. 17.5 P 114/98 PA=O_2 cont. 23.9 P 114/86 O_2 step-up in RV	No	First diagnosed as Eisenmenger. 1947 artificial ASD. Vessel position at operation typical
(3) A-66583 E.J. Male	27 yr., 1949	Since birth 3 plus 2 plus No	Systolic LSB, diastolic. No	RBC 8.55 Hb. 23 Het. 72	Prominent pul. conus, increased pul. vascularity	Simultaneous filling of aorta and pul. artery. Pulmonary artery and aorta side by side	PA systemic pressure and highest O_2 content. Ao=O_2 cont. 21.4 PA=O_2 cont. 27.0 O_2 step-up in RV	No	Angio and cath. data offer good evidence of Taussig-Bing
(4) A-66655 M.H. Female	6 yr., 1949 8 yr., 1951	Since birth 3 plus 2 plus No	Systolic, LSB No	RBC 10.25 Hb. 25 Het. 82.4	Full, prominent pul. conus, increased pul. vascularity	Aorta more anterior as normal and in lateral, side by side to pul. artery	Pul. artery not entered	Both vessels side by side. Large VSD and overriding pulmonary artery	Died at operation for artificial ASD
(5) A-74720 I.B. Female	4 yr., 1949 6 yr., 1951	Since birth 2 plus 1 plus No	Harsh syst., LSB No	RBC 7.6 Hb. 20 Het. 53	Prominent pul. conus, increased pul. vascularity	Both vessels side by side	PA higher O_2 cont. than FA PA=16.88 P=104/90 FA=13.63 O_2 step-up in RV	No	Cath. and angio. conclusive
(6) A-94158 H.D.S. Male	1 yr., 1951 2 yr., 1952	Since birth 2 plus 1 plus Yes	Systolic, LSB No	RBC 4.94 Hb. 9 Het. 38	Full pul. conus, increased pul. vascularity	Aorta more anterior as normal	PA higher O_2 cont. than FA PA=12.9 P=160/75 FA= 8.8 O_2 step-up in RV	No	Cath. and angio. conclusive. Anemic
(7) A-98536 W.W. Male	4 mo., 1952 6 yr., 1958	Since birth 3 plus 2 plus No	Systolic, LSB No	RBC 7.12 Hb. 19 Het. 59	Full pulmonary conus, increased pul. vascularity	Typical vessel position. Aorta and pul. artery side by side	Pul. artery not entered	No	1956 artificial ASD. At operation, vessel position thought to be typical
(8) B-2427 G.L.P. Male	12 da., 1953 4½ mo., 1953	Since birth 3 plus No	Systolic, LSB No	RBC 6.42 Hb. 14.9 Het. 56	Full pulmonary conus, increased pul. vascularity	Aorta and pul. artery side by side	No	Aorta off right vent. PA anterior & overriding a large VSD. Muscular ridge as described by	Typical case
B-12931 I.M.V.	2½ yr., 1957	1 plus None	No	Hb. 13.2 Het. 44	conus, increased pul. vascularity	position. Good PA view			clusive

B-12931	2½ yr., 1957	1 plus	No	Hb. 13.2	conus, increased	position. Good			
I.M.V.		None		Het. 44	pul. vascularity	PA view			
Female		No							
(12)	[illegible]	Since birth	Systolic, LSB	RBC 6.0	Prominent pul.	ASD good in lat.	No	No	[illegible]
B-39688	2 yr., 1958	3 plus	Faint	Hb. 16.4	conus, increased	Typical Taussig-			at angio.
I.R.St.		2 plus		Het. 59	pul. vascularity	Bing position			
Female		No							
(11)	5 yr., 1946	Cyan. 1 mo.	Systolic, LSB,	RBC 7.48	Very prominent	No	No	Typical Taus-	Clinically diag-
A-51911	10 yr., 1951	3 plus	mid-diastolic	Hb. 21	pul. conus, and			sig-Bing.	nosed; con-
G.H.T.		2 plus	No	Het. 64.5	increased pul.			Large PA	firmed at
Female		No			vascularity			anterior,	autopsy
								overriding	
								VSD. PDA	
(12)	2 yr., 1947	Since birth	No	RBC 8.7	Prominent pul.	Inconclusive	PA higher O_2 cont. than FA	No	1949 artificial
A-56231	10 yr., 1955	3 plus	No	Hb. 19.8	conus, increased		PA=24.85 P=92/80		ASD. At opera-
C.E.G.		2 plus		Het. 66.2	pul. vascularity		FA=18.25		tion, vessel po-
Male		No					O_2 step-up in RV		sition thought
									to be typical
(13)	3 yr., 1946	Since birth	Systolic, LSB	RBC 7.40	Prominent pul.	No	PA higher O_2 cont. than FA	No	First diagnosed
A-52036	15 yr., 1958	2 plus	No	Hb. 17.5	conus, increased		and Ao.		as Eisenmenger.
A.M.S.		1 plus		Het. 61	pul. vascularity		Ao=15.6		Good evidence
Female		No					PA=16.88 P=88/50		at cath.
(14)	10 mo., 1958	Since birth	Systolic, LSB	RBC 5.9	Prominent pul.	In right lateral,	Pul. artery not entered	No	Angio. con-
B-48029	1½ yr., 1958	2 plus	Systolic	Hb. 13.9	conus, increased	typical vessel			clusive
D.G.		1 plus		Het. 50	pul. vascularity	location			
Male		No							

Growth and development were slow. On physical examination, 1 patient had no murmur and 3 had a systolic murmur along the left sternal border, loudest at the third and fourth left intercostal spaces. One patient had a mid-diastolic murmur. Two patients had systolic thrills, and 1 was reported to have had spells of unconsciousness. All had right axis deviation and right ventricular hypertrophy or preponderance in the electrocardiogram. X-ray and fluoroscopy showed that the hearts were moderately or markedly enlarged; each showed very prominent pulmonary conus and increased pulmonary vascularity. There was 1 patient with a right aortic arch. The clinical findings were so similar to the findings of the Taussig-Bing transposition that special studies were carried out.

The data obtained at cardiac catheterization in patients 2 and 4 were identical to those in the Taussig-Bing group, with the highest oxygen content in the pulmonary artery and the pressures at systemic level. Spot films were not taken at catheterization but the course of the catheter was described. The catheter seemed to enter a posterior pulmonary artery. In case 3 the pulmonary artery was not entered and hence catheterization could not establish the diagnosis. In the cases with angiocardiography, this test established the differential diagnosis. In cases 1, 2, and 4, the aorta was seen to arise anterior to the pulmonary artery. The opacification of the aorta was usually better than that of the pulmonary artery.

Discussion

In 1949 Taussig and Bing published their original case of complete transposition of the aorta with a levoposition of the pulmonary artery.[8] This case had been studied by cardiac catheterization, angiocardiography, and autopsy. The authors gave a clear picture of the clinical and physiologic findings and their anatomic explanation. The characteristics of this malformation are: 1. The origin of the aorta is from the right ventricle, but it lies to the right of the pulmonary artery and is not anterior to it as in the usual complete transposition of the great vessels. 2. The pulmonary artery, although in its approximate normal position, overrides a ventricular septal defect. 3. Right ventricular hypertrophy and an anterior deviation of the ventricular septum. 4. A muscular ridge separates the origin of the 2 great vessels. Consequently, in this malformation most of the venous blood that enters the right ventricle is directed into the aorta, and most of the pulmonary venous blood that en-

Figure 5

Plain x-ray Taussig-Bing transposition. Case 7. Top, *anteroposterior view;* middle, *left anterior oblique view;* bottom, *right anterior oblique view.*

ters the left ventricle is directed into the pulmonary artery. Physiologically this malformation is characterized by a higher oxygen content in the pulmonary artery than in the right ventricle and in the aorta. There is systemic pressure in the pulmonary artery.

At the time of the first publication, the existence of a second transposition with overriding pulmonary artery with the same abnormal physiology had not been reported. In the Taussig-Bing heart, both great vessels are side by side, whereas in the second type of transposition with overriding pulmonary artery, the great vessels are completely transposed; that is, the pulmonary artery lies behind the aorta (figs. 4, 8, and 9). During recent years, no clear-cut separation has been made between these 2 anatomically different malformations; in several publications the latter malformation was considered as Taussig-Bing transposition.[1, 10, 12, 14] Keith[21] published in 1958 drawings of the 2 different transpositions and pointed out that they are not identical. He even separated the 2 malformations in regard to life expectancy and prognosis.

It may be pointed out that in these anatomically different types of transpositions, the terms "complete" or "incomplete" transposition of the great vessels may have 2 different meanings. First, the terms "complete" or "incomplete" are used to stress that a vessel originates completely or incompletely from the opposite ventricle. In this sense, both transpositions under discussion are incomplete transpositions because of the biventricular origin of the pulmonary artery. Secondly, the terms "complete" or "incomplete" may be used in order to characterize the relation of the 2 great vessels to each other. In this case, the original Taussig-Bing heart again is an incomplete transposition but the transposition with posteriorly placed overriding pulmonary artery is a complete transposition. Keith[21] seems to prefer the second point of view, since he used the term "complete" transposition for the latter group and "incomplete" for the Taussig-Bing heart. This differentiation appears to be useful, despite the fact that the pulmonary artery is overriding the ventricular septal defect and is biventricular in origin

in both instances. Furthermore, the relation of the 2 vessels to each other is of greater diagnostic importance than the biventricular origin of the pulmonary artery.

The patients included in this study all had a history and clinical findings characteristic of transposition of the great vessels. The outstanding findings that permit the suggestive diagnosis of a Taussig-Bing transposition are the x-ray and fluoroscopic findings. As Taussig in a clinical analysis of complete transposition has pointed out,[7] the vascular shadow is narrow in the posteroanterior view and widens in the left anterior oblique view. This sign is present only if the transposition of the great vessels is complete and the counterclockwise rotation is 180 degrees and both great vessels are of normal size. If there is a very prominent pulmonary artery segment and a wide vascular shadow, the differential diagnosis lies between a Taussig-Bing transposition or a transposition with dilated posterior pulmonary artery. The decision whether cardiac catheterization or angiocardiography is superior in establishing the correct diagnosis is a difficult one. Catheterization data may offer a clue as to the diagnosis of a Taussig-Bing transposition provided the pulmonary artery is entered and the oxygen content is higher than in the aorta. This finding alone does not differentiate between the 2 types of transposition. At cardiac catheterization, either a spot film taken in the posteroanterior or right oblique view with the catheter in the pulmonary artery, or the observation of the course of the catheter is necessary in order to differentiate the position of the vessels. The catheterization data should show a step-up in oxygen content of several volumes per cent in the right ventricle, (6 volumes per cent in the original case) and a lower oxygen content in the aorta than in the pulmonary artery. In the original case the oxygen content in the pulmonary artery was 4.4 volumes per cent higher than that in the right ventricle and 7.6 volumes per cent higher than that in the aorta. This has been a constant finding in our series of cases.

Angiocardiography usually gives clear information about the position of the great vessels. The posteroanterior and right lateral projection are the most informative ones. In this study, angiocardiography usually showed better opacification of the aorta than of the

Figure 6

Top. *Lateral angiocardiogram of the original Taussig-Bing case.* Bottom. *Anteroposterior angiocardiogram of the original Taussig-Bing case.*

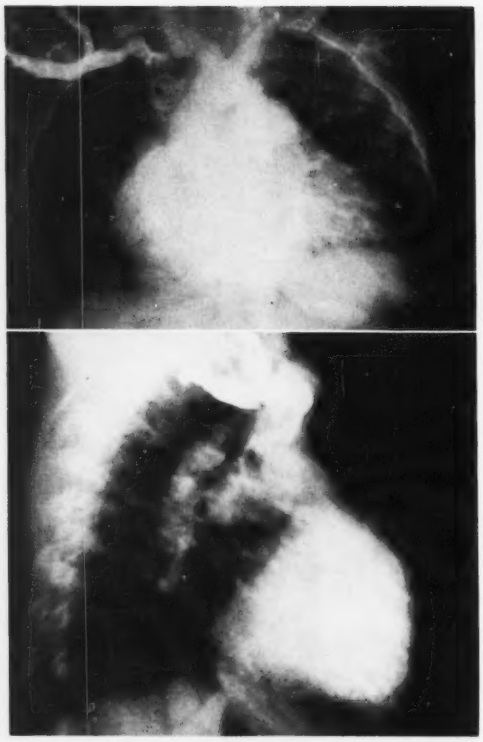

Figure 7

Angiocardiogram Taussig-Bing transposition. Case 7. Top, *anteroposterior view;* bottom, *lateral view. Note in lateral view that aorta is in same position as in original Taussig-Bing heart, shown in figure 6. The aorta is not so far anterior as in complete transposition (see fig. 9).*

pulmonary artery. Furthermore, the position of the aorta is so different in the Taussig-Bing heart from that in complete transpositions and also in a transposition with posteriorly placed pulmonary artery, that a differentiation is usually possible. In the latter, the pulmonary artery may show only diffuse filling and if it is dilated, its shadow may even be seen to extend beyond the aorta anteriorly and posteriorly in the lateral view. As previously pointed out by Taussig,[7] the shadow of the pulmonary conus is absent in the usual type of complete transpositions because the aorta seldom arises so far anteriorly and to the left as does the normal pulmonary artery; this observation has been confirmed on angiocardiography. Several of the angiocardiograms of complete transpositions published by Cooley and Sloan[20] demonstrate that the shadow of the pulmonary conus is absent. Owing to the normal position of the pulmonary artery and its biventricular origin, this sign is not present in the Taussig-Bing hearts. According to Cooley and Sloan, the most reliable angiocardiographic findings for the diagnosis of complete transposition is the immediate filling of an anteriorly placed aorta with high concentrations of contrast medium. They pointed out that on fluoroscopy in patients with complete transpositions it may be possible to see large pulsating pulmonary arteries, although angiocardiograms only show faint filling of these vessels. These authors stated that the pulmonary artery should be better seen when it overrides as in the Taussig-Bing heart than in the usual transposition. Without doubt, there is a possibility of better filling of the pulmonary artery but this may depend to a large extent upon the size of the pulmonary artery and the dilution of the contrast medium in this vessel. The most significant finding, however, was a full pulmonary conus in contrast to its absence in the complete transpositions. A full pulmonary conus is found in the Taussig-Bing hearts and does occur in the transpositions with posteriorly placed pulmonary artery when this artery is so huge and so dilated that its shadow fills the area normally occupied by the pulmonary conus. There would be less dilution of the contrast medium in the pulmonary artery if it were injected into the left ventricle by the method of Uricchio.[22] Thus, direct injection into the left ventricle may give the best opacification of both great vessels in this malformation.

The differentiation of the Taussig-Bing transposition from a complete transposition with a large ventricular septal defect is possible if both angiocardiography and cardiac catheterization are carried out. The plain x-ray and spot films taken during catheterization and angiocardiography in the anteroposterior and lateral projection are the most helpful means of differentiation.

This malformation also requires differentiation from a single ventricle with transposition

Data of Four Cases of Complete Transposition with Overriding, Posterior Pulmonary Artery

Case no., sex	Age last ex.	Cyanosis, spells	Murmur, thrill	Blood count	X-ray	Angiocardiogram	Catheterization	Autopsy	
(1) A-70174 P.H. Female	3 mo., 1949	Since birth 1 plus No	Systolic, LSB No	RBC 4.9 Hb. 14.5 Het. —	Full pulmonary conus, increased pul. vascularity. Right aortic arch	Aorta arising far anteriorly	No	Complete transposition with posteriorly placed, overriding PA. Single cor. artery	Died at operation for artificial ASD
(2) A-52845 B.J.H. Female	5 yr., 1947	Since birth 3 plus 2 plus No	Systolic, LSB, diastolic No	RBC 8.78 Hb. 19.3 Het. 72	Prominent pul. conus, increased pul. vascularity	No	Highest O_2 content in PA PA=23.3 P=68/35 FA=18.6 P=99/62 O_2 step-up in RV	No	At operation for artificial ASD the aorta was seen to arise far anteriorly
(3) A-56164 E.C.P. Male	6 yr., 1947	Since birth 3 plus 2 plus No	No No	RBC 9.14 Hb. 24 Het. 75	Prominent pul. conus, increased pul. vascularity	Aorta arising far anteriorly	Pul. artery not entered	Complete transposition with large, posteriorly placed, overriding PA	Typical case
(4) A-73852 G.W. Male	5 mo., 1949 6 mo., 1949	Since birth 3 plus No	Systolic, LSB Slight	RBC 6.27 Hb. 16 Het. 61	Prominent pul. conus, increased pul. vascularity	Aorta arising far anteriorly	Highest O_2 content in PA PA=13.39 P=92/84 FA= 3.70 O_2 step-up in RV	Complete transposition with large, posteriorly placed, overriding PA	First diagnosed as Taussig-Bing. Died at operation for artificial ASD

if the position of the vessels is not that of a 180-degree counterclockwise rotation, especially if the aorta is rotated further to the left than usual. The anteroposterior angiocardiogram usually offers evidence that a ventricular septum exists in the Taussig-Bing transposition. A very large step-up in oxygen content in the right ventricle has no real value in the differentiation of a single ventricle with transposition from a Taussig-Bing heart, since in the original Taussig-Bing case there was a step-up of 6 volumes per cent. According to Keith,[21] the course of the catheter in the ventricle and the great variation in oxygen content in serial samples from one area, which is frequently found in single ventricle, may be helpful.

There is probably no difference in the incidence of associated lesions in complete transpositions and in the Taussig-Bing transposition. The most common one is atrial septal defect; coarctation of the aorta has also been reported. An atrial septal defect is usually easily demonstrated on lateral angiocardiograms. In the present series there was no case with a coarctation of the aorta.

The pulmonary vascular lesions were carefully studied in 2 of the autopsied Taussig-Bing hearts and in 2 of the cases with posteriorly placed pulmonary artery. Both Taussig-Bing cases had medial hypertrophy and intimal proliferations and one had "dilatation lesions" similar to those described by Heath and Edwards[23] as grade-5 lesions in cases with large ventricular septal defects. In the 2 cases of complete transposition with posteriorly placed pulmonary artery, only medial thickening of the pulmonary arterioles is described. This seems to support Keith's view that the Taussig-Bing transposition tends to develop such pulmonary vascular lesions whereas the other type does not.[21] Actually there is no reason for any difference in pathology in this respect, since in both the pulmonary vessels received blood through a common ejectile force.[23, 24] The development of such pulmonary vascular lesions depends on the duration of life. The observation that the patients with the Taussig-Bing transposition usually lived

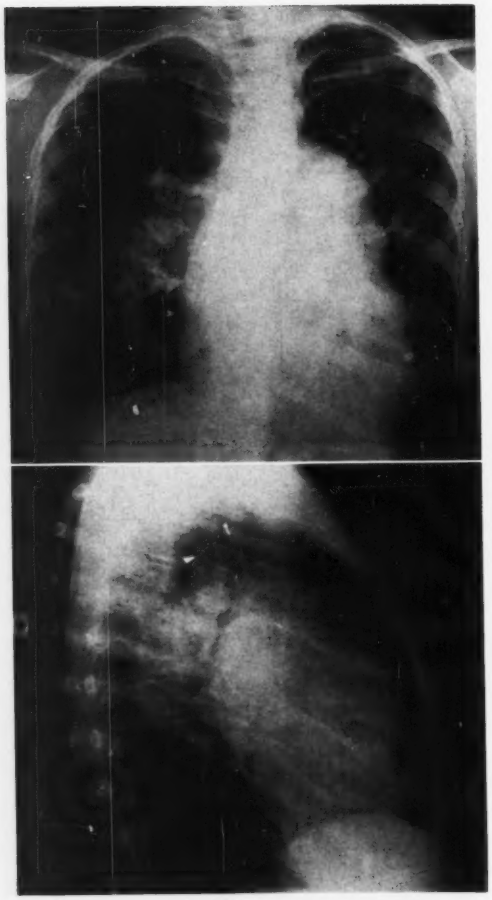

Figure 8

Posterior pulmonary artery. Case 2, table 2. Plain x-ray: Top, *anteroposterior view;* bottom, *lateral view.*

longer may explain the occurrence of these lesions.

Since fluoroscopy so often gives a clue in the diagnosis of congenital heart disease, it may be expected that such a fundamental difference in the position of the great vessels as is found in these 2 transpositions can be differentiated during fluoroscopic observation. In order to demonstrate the projection of the shadow of the great vessels upon the screen of the fluoroscope, the drawings of the normal heart and the 2 malformations in figures 2, 3, and 4 were made. The lines beginning at the origin of the 2 vessels show how these vessels are projected upon the plane of the screen. In the posteroanterior view, the Taussig-Bing heart has a wide vascular shadow with a prominent pulmonary segment, since both vessels are side by side. In the transposition with a posterior pulmonary artery, the vascular shadow may also be wide because of the huge pulmonary artery. The usual position of the pulmonary segment may be occupied by the aorta as shown in figure 4, or it may be very prominent due to the large posterior pulmonary artery. Thus, it may be difficult on fluoroscopy in the posteroanterior projection to decide whether the vessel occupying the pulmonary segment is the aorta or the pulmonary artery. If the 2 vessels are side by side, as in the Taussig-Bing heart, it is quite obvious that in the right anterior oblique view the left vessel, which in this instance is the pulmonary artery, is in front and in the left anterior oblique view, the right vessel (aorta), is in front. Since in this particular case the pulmonary artery is usually the larger vessel, in the lateral views its shadow may extend beyond the aorta anteriorly. Metianu[13] mentioned in his publication of a Taussig-Bing heart that there was a very prominent vascular shadow in the right anterior oblique view. He pointed out that this shadow may be a pulmonary artery but an anteriorly displaced aorta could not be excluded. In the photograph of the specimen, which certainly is a Taussig-Bing heart, it can be seen that this vessel indeed was the pulmonary artery. Figure 3 shows how far anteriorly the shadow of this vessel may be projected in the right anterior oblique view. In the left anterior oblique view, however, figure 3 shows clearly that the aorta is projected anteriorly in this position. In contrast, as is shown in figure 4, in the transposition with posteriorly placed pulmonary artery, the projection of the aorta upon the screen is always anterior to the pulmonary artery. In this type of transposition, in the left anterior oblique view the anterior border of the 2 vessels may be only slightly separated and the huge pulmonary artery usually dominates the picture. Thus, these differences in x-ray projec-

on of the great vessels may be helpful on fluoroscopy as well as on angiocardiography.

The clear differentiation between the Taussig-Bing transposition and a complete transposition with posteriorly placed overriding pulmonary artery may be a most difficult problem. Differential diagnosis during life is possible if on angiocardiography the position of the aorta is typical of either malformation or if there is sufficient opacification of the pulmonary artery. Gasul[25] pointed out that the differential diagnosis on angiocardiography in this group of transpositions may be so difficult that he included the complete transpositions with large ventricular septal defects in the Taussig-Bing group. The example of a Taussig-Bing angiocardiogram published by Gasul certainly is that of a complete transposition with posteriorly placed pulmonary artery. In the angiocardiogram published by Adams and Kaplan[26] as a Taussig-Bing heart, the aorta lies far anterior to the pulmonary artery and the 2 vessels are not side by side as in the Taussig-Bing heart. Kjellberg, Mannheimer, et al.[27] reported in their series 3 patients with a Taussig-Bing transposition; in one instance this malformation was associated with a coarctation of the aorta. One angiocardiogram published by these authors also shows a posterior pulmonary artery. Chiechi[1] in his critical review article on this subject added 4 autopsied cases of his own. As he pointed out and as can be seen in the photographs of his paper, the aorta was far anterior to the pulmonary artery in cases 1 and 2. The 180-degree counterclockwise rotation of the pulmonary artery in his case 1 is the reason that the plain x-ray of this case is not the typical x-ray of the Taussig-Bing heart. The relationship of the 2 great vessels to each other is not mentioned in the remaining 2 cases. Thus, in 2 of his cases the position of the vessels was not like that in the Taussig-Bing transposition. Furthermore, Chiechi does not mention the 2 anatomically different types of transposition that are identical in regard to their physiology. Case 1 of the report by Van Buchem[10] has a posterior pulmonary artery. The case reported by Martin and Lewis[12] also has a

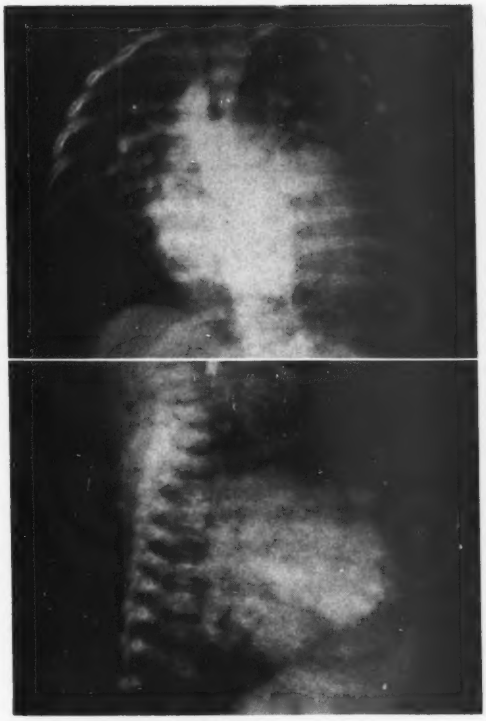

Figure 9

Posterior pulmonary artery. Case 1, table 2. Angiocardiogram: Top, *anteroposterior view;* bottom, *lateral view.*

posterior pulmonary artery. The same position of the vessels is present in the 2 cases of Maxwell and Crumpton.[14] In contrast to the above reports, the case published by Lev and Volk[9] is certainly a typical Taussig-Bing heart. The vessels are side by side in this specimen. An interesting case was published by Falholt and Pedersen[17] in 1952. This case was diagnosed by cardiac catheterization. There was a very full and prominent pulmonary conus on x-ray. At catheterization both the pulmonary artery and the aorta were entered and the oxygen content in the pulmonary artery was highest. The authors mentioned that this would not exclude a transposition with large ventricular septal defect, but at cardiac catheterization the catheter was seen to enter the pulmonary artery directly from the right ventricle in a straight course probably through an over-

Table 3

Distribution of the Seventy-three Reviewed Cases with Posssible Taussig-Bing Transposition in the Cardiac Clinic, Johns Hopkins Hospital

Taussig-Bing transpositions	
	3 proved by autopsy
	1 exact position of great vessels not mentioned in autopsy report
	11 diagnosed by catheterization, angiocardiogram, or both
	17 clinically diagnosed, not proved
Complete transpositions with posteriorly placed, overriding pulmonary artery	
	3 proved by autopsy
	1 diagnosed by catheterization
	3 clinically diagnosed, not proved
Complete transposition with ventricular septal defect	
	7 with catheterization data similar to Taussig-Bing transposition
Data incomplete	
	25 cases
Others	
	1 single ventricle
	1 dextrocardia with incomplete transposition

riding pulmonary orifice. The pulmonary artery was located at its normal place. Thus, this is a true Taussig-Bing transposition.

As pointed out above, with the aid of cardiac catheterization or angiocardiography a differential diagnosis between the transposition as originally described by Taussig and Bing and the transposition with a posterior overriding pulmonary artery may be possible during life. Frequently it is necessary to perform both cardiac catheterization and angiocardiography. The differential diagnosis is desirable from a clinical point of view and accurate anatomic classification will be of great importance if total correction of these 2 malformations becomes possible.

A detailed discussion of the theories of embryologic development of transposition of the great vessels is not a subject of this paper. Theories about the development of transpositions have been published long before clinical diagnosis was attempted. These theories do not aid in the clinical approach but are of considerable interest. The modification of Spitzer's theory[5] by Lev and Saphir[28] seems to be a plausible compromise betwen Spitzer's phylogenetic theory and the ontogenetic theory of Pernkopf and Wirtinger.[29] According to the latter authors, at the end of the first phase of the bulbar ridges and their absorption into the ventricle that are responsible for the twist formed, the bulbar ridges and the atrial region are already twisted, whereas the truncus is still a straight tube. During the second phase, a torsion occurs at the bulbus-trancus ostium and a "backtorsion" in the region of the ventriculobulbar junction. It is the twist of the bulbar ridges and their absorption into the ventricle that are responsible for the twisting of the great vessels and their correct position. It is the opinion of Lev and Saphir that the bulbar ridges may be malformed; thus the hemodynamic forces postulated by Spitzer cause an abnormal absorption of the bulbus. Consequently, the hemodynamic forces could lessen the degree of torsion of the ostia to any possible extent and thus cause the various forms of transpositions. It also would explain the hyperplasia of either one of the great vessels as, for instance, the hyperplasia of the pulmonary artery in the Taussig-Bing heart.

Summary

The Taussig-Bing transposition bears the name of the authors who described for the first time the clinical, physiologic, and anatomic findings. It has been recognized that the malformation is physiologically not so distinct as it is anatomically and that a transposition with the same physiologic pattern but different anatomy has been observed. Several case reports have appeared in the literature in which no clear differentiation was made in regard to the second type of transposition with overriding pulmonary artery. In the latter instance there is a complete transposition of both great vessels with a posteriorly placed overriding pulmonary artery in contrast to the original Taussig-Bing heart in which the 2 vessels are side by side, the pulmonary artery being in its normal place.

Following the original case report, 14 cases were seen in this clinic in which the diagnosis

was established either by catheterization, angiocardiography, or autopsy. In 4 other cases, the diagnosis of a transposition with a posterior overriding pulmonary artery was made. Criteria for the differential diagnosis of these 2 lesions are pointed out. The differentiation of these 2 transpositions is of particular importance for possible surgical correction.

Appendix

Summary of the Autopsy Reports of the Taussig-Bing Cases

Case 4: J.H.H. Autopsy No. 23083, performed by Dr. Reynolds. Autopsy showed the typical position of the great vessels as seen in Taussig-Bing hearts, the pulmonary artery and aorta being side by side. The pulmonary artery overrode a large ventricular septal defect. The pulmonary valve was bicuspid. There was also a muscular ridge similar to that in the original case. The coronary arteries were normal. The medial and smaller pulmonary arteries showed thrombi in various stages of organization and recanalization. There was marked intimal proliferation. The smallest arteries and capillaries were enormously dilated. No additional lesions beside the surgically created atrial septal defect were present.

Case 8: J.H.H. Autopsy No. 24472, performed by Dr. Bunnell. The pulmonary artery and aorta were side by side and the pulmonary artery overrode a large ventricular septal defect. A muscular ridge separated the origin of the 2 great vessels. The coronary arteries were normal. There is no description of changes in the pulmonary vessels.

Case 11: J.H.H. Autopsy No. 23098, performed by Dr. Iber. The patient died 3 days after the creation of an atrial septal defect. Autopsy showed a probe-patent foramen ovale. The artificial atrial septal defect measured 2.5 cm. in diameter. There was marked right ventricular hypertrophy. The aorta arose side by side to the pulmonary artery. It came off the right ventricle. The pulmonary artery arose from the left ventricle and definitely overrode a ventricular septal defect of 2.5 cm. in diameter. The aortic and pulmonary artery leaflets were normal. The pulmonary artery at its origin measured 8.7 cm. in circumference, the aorta 4.5 cm. The coronary arteries were normal. The ductus arteriosus was patent. The pulmonary arterioles were thickened and showed intimal proliferation.

Summary of the Autopsy Reports of the Cases with Posterior Pulmonary Artery

Case 1: J.H.H. Autopsy No. 501909, performed by Dr. Berthrong. There was a surgically created atrial septal defect of 1.2 cm. in diameter and inferior to that another atrial septal defect of 1 cm. in diameter, which was present prior to operation. The right ventricle was hypertrophied and the aorta came off the right ventricle, anterior to the pulmonary artery. The aortic valve had 3 cusps. There was only 1 coronary artery, branching directly toward the right ventricle as well as circumflex branches passing in both directions in the atrioventricular groove. The aorta arched to the right and descended on the right. The pulmonary artery arose posteriorly from the left ventricle and overrode a ventricular septal defect of 1.2 cm. in diameter. The ventricular septal defect was directly beneath the pulmonary valve ring. The pulmonary artery was greatly dilated. The pulmonary arterioles showed thickening of the media.

Case 3: J.H.H. Autopsy No. 428660, performed by Dr. Brown. Autopsy showed the aorta approximately in the normal position of the pulmonary artery and the pulmonary artery posterior to the aorta. The pulmonary artery overrode a ventricular septal defect of 3 by 1.5 cm. There was no crista or muscular ridge.

Case 4: J.H.H. Autopsy No. 22095, performed by Dr. Wolfson. There was a surgically created atrial septal defect. The foramen ovale was sealed. The right ventricular wall was thick (18 mm.) and its chamber was dilated. The aorta arose from the anterior part of the right ventricle. The aortic valve was normal, its ring measuring 3 cm. in circumference. The coronary arteries were normal. Immediately behind the aorta the crista appeared; it was a good-sized muscular band but was incomplete. The inferior margin led to a ventricular septal defect of 1 by 1 cm. in diameter. The left ventricle measured 8.5 mm. in thickness. From the left ventricle arose the pulmonary artery and overrode the ventricular septal defect by 20 per cent. Its valve ring measured 3.3 cm. in diameter, the main pulmonary artery 3.8 cm., and the left pulmonary artery was greatly dilated, measuring 20 cm. in diameter. There was a probe-patent ductus arteriosus. The pulmonary vessels were thickened.

Acknowledgment

The author wishes to express his sincerest thanks and appreciation to Drs. Helen B. Taussig, Richard J. Bing, and Charlotte Ferencz for the invaluable help and many discussions during the course of this study.

Summario in Interlingua

Le transposition de Taussig-Bing porta le nomine del autores del prime description del constatationes clinic, physiologic, e anatomic characteristic de illo. On ha notate que iste malformation es minus distincte physiologicamente que anatomicamente e que

il occurre un transposition con le mesme complexo de manifestationes physiologic sed un differente configuration anatomic. Plure reportos de casos se trova in le litteratura in que nulle precise differentiation esseva facite inter le transposition de Taussig-Bing e le altere typo de transposition in que le arteria pulmonar se distingue per su disbordamento posterior. In le secunde del duo situationes il ha un transposition complete del duo grande vasos con disbordamento posterior del arteria pulmonar, per contrasto con le syndrome de Taussig-Bing in que le duo vasos es placiate in juxtaposition con le arteria pulmonar in sito normal.

Post le caso del reporto original, 14 exemplos de corde de Taussig-Bing esseva observate a iste clinica, con diagnoses establite per catheterismo, per angiocardiographia, o al necropsia. In 4 casos additional, le diagnose esseva transposition con disbordamento posterior del arteria pulmonar. Es signalate criterios pro le diagnose differential de iste 2 lesions. Le importantia de un correcte differentiation es apparente ab le puncto de vista de un possibile correction chirurgic.

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Medical Eponyms

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Bowman's Capsule. William Bowman (1816-1892) F.R.S., Assistant Surgeon to the King's College Hospital, and Demonstrator of Anatomy in King's College, London, read before the Royal Society on February 17, 1842, a paper "On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation through that Gland." This was printed and may be found in the *Philosophical Transactions of the Royal Society of London* for the year 1842, part I, pp. 57-80 (vol. 132).

"The Malpighian bodies I saw to be a rounded mass of minute vessels invested by a cyst or capsule (first particularly pointed out by MÜLLER, who conceives it to be perfectly closed, except at one point where perforated by the vessels) of precisely similar appearance to the basement membrane of the tubes. Seeing these similar tissues in such close proximity, it was not easy to resist the conviction that the capsule was the basement membrane of the tubes expanded over the vessels. . . . Having, during last summer, been made acquainted, through the kindness of DR. MILNE EDWARDS, with a new method of injection employed with great success by M. DOYÈRE of Paris." (This consists of two fluids which mingle in the small vessels, and cause a precipitation there. The best fluids are saturated solutions of bichromate of potass and of acetate of lead. They are injected in succession through the same vessel, whence the method is termed that by *double injection*. KRAUSE published an account of it two years ago, but M. DOYÈRE appears to have arrived at it after a laborious trial of numerous solutions. Both deserve the thanks of anatomists for so valuable an addition to the means of investigation.)—I injected some kidneys through the artery, by this method, in order to notice the nature of the vascular ramifications in the Malpighian bodies. I not only found what I sought, but the clearest evidence that the capsule which invests them is, in truth, the basement membrane of the uriniferous tube expanded over the tuft of vessels."

Prognostic Significance of Raynaud's Phenomenon and Other Clinical Characteristics of Systemic Scleroderma

A Study of 271 Cases

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THE CLASSIFICATION of scleroderma has been a controversial subject primarily because adequate follow-up studies have been lacking. It is generally agreed that localized forms of scleroderma such as morphea and linear scleroderma are not progressive or systemic diseases and have a good prognosis. The same is true for scleroderma confined to the fingers and toes of patients with long-standing Raynaud's disease (sclerodactylia). It is in the classification of generalized or systemic scleroderma that confusion has arisen. In 1943, O'Leary and Waisman[1] advocated perpetuation of the term "acrosclerosis" first proposed by Hutchinson[2] and favored by Sellei.[3] These workers considered acrosclerosis to be a relatively benign and only slowly progressing form of generalized scleroderma with Raynaud's phenomenon as a constant and usually prominent clinical feature. The prognosis in acrosclerosis was considered favorable when contrasted with that in "generalized progressive scleroderma," in which the cutaneous changes usually appeared first on the trunk rather than acrally and in which Raynaud's phenomenon was absent or minimal. Generalized progressive scleroderma was described by O'Leary and Waisman as a fulminating disease, usually culminating in death within 2 years.

In studies of Raynaud's phenomenon and Raynaud's disease among women and girls[4, 5] many patients with Raynaud's phenomenon secondary to scleroderma (acrosclerosis) were found to have died; since this observation was contrary to the reputed good prognosis for patients with acrosclerosis, the present study was undertaken to correlate clinical findings, especially Raynaud's phenomenon, with prognosis in patients with generalized scleroderma.

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Read at the Thirty-second Annual Scientific Sessions of the American Heart Association, Philadelphia, Pa., October 23, 1959.

Material and Methods

The case records of all patients with scleroderma seen at the Mayo Clinic from January 1, 1945, to December 31, 1952, were reviewed and only those in which the diagnosis was first made during this period were included. There were 488 patients. The cases with only localized scleroderma (linear scleroderma, morphea, hemiatrophy, and sclerodactylia secondary to Raynaud's disease) were excluded. This left a total of 271 patients with generalized scleroderma (acrosclerosis or generalized progressive scleroderma) for whom the diagnosis was made during this 8-year period. Almost all of the patients were examined by consultants in the sections of dermatology or peripheral vascular diseases or both and an attempt had usually been made to designate the type of scleroderma according to O'Leary and Waisman's classification.[1] Most patients were considered to have acrosclerosis. The data from these 271 records were analyzed, and follow-up information was obtained by letter or by re-examination at the clinic.

Clinical Characteristics

Most of the 271 patients (73.4 per cent) were women and the average age at the time of diagnosis for the entire group was 42.9 years; for women it was 41.9 years, and for men 45.7 years (table 1). Raynaud's phenomenon was present at some time during the course of the disease in 220 patients (81.2 per cent) and it was the initial symptom in 88 (table 2). In some cases, it was difficult to determine whether or not Raynaud's phenomenon preceded the cutaneous sclerosis, as the

Table 1

ge of 271 Patients at Time of Diagnosis of ystemic Scleroderma

ge, years	Women		Men	
	Number	Per cent	Number	Per cent
0 — 20	7	3.5	3	4.2
1 — 30	31	15.6	8	11.1
1 — 40	55	27.7	16	22.2
1 — 50	51	25.6	14	19.5
1 — 60	40	20.1	23	31.9
1 or more	15	7.5	8	11.1
Total	199	100.0	72	100.0
Average age	41.9 years		45.7 years	
Both sexes	42.9 years			

Table 2

Initial Symptoms of 271 Patients with Systemic Scleroderma

Symptom	Number	Per cent
Raynaud's phenomenon	88	32.5
Scleroderma of hands*	132	48.7
Scleroderma of extremities or face but not of hands	19	7.0
Scleroderma of trunk	7	2.6
Generalized stiffness of joints	14	5.2
Trophic changes of fingers (ulceration, fissuring, chronic paronychias)	5	1.8
Pigmentation	3	1.1
Dysphagia	2	0.7
Dyspnea	1	0.4

*Many patients described this as "swelling" of the hands.

more spectacular vasospastic symptoms were often more noticeable to the patient than a mild degree of sclerosis. Patients seen shortly after the onset of Raynaud's phenomenon frequently were found to have sclerodermatous changes which they had overlooked. In 132 the first symptom was stiffness or swelling of the hands. Five patients first noted trophic changes of the fingertips. Thus the first symptoms were referable to the hands in 83.0 per cent of the patients. Scleroderma on the trunk, a cardinal feature of O'Leary and Waisman's description of generalized progressive scleroderma, was noted as an initial symptom by only 2.6 per cent of our patients.

The involvement or complications at the time of the original diagnosis at the clinic are listed in table 3. "Trophic changes" refer to ulcerations, fissures, or chronic paronychias involving the fingertips. Pigmentation was noted in 45.0 per cent of the cases and frequently consisted of a generalized dusky-brown discoloration, usually more prominent in regions of sclerosis. As a result of this, the diagnosis of Addison's disease was entertained for several patients who had associated weakness and hypotension. Only 10.0 per cent of the patients had associated calcinosis cutis, and it usually involved the fingers and hands. Less often the deposits were found in the skin overlying the elbows or on the buttocks.

The trophic changes of 4 patients were severe enough to result in gangrene requiring amputations of one or more digits. No major amputations were necessary. Sympathectomy was carried out on 24 patients, being cervicothoracic in 19, lumbar in 1, and both in 4. Some of the patients had been operated on in the belief that the condition represented Raynaud's disease with sclerodactylia and some were operated on prior to the time of diagnosis of scleroderma at the clinic.

Studies of esophageal motility were not being done at the time these patients were examined, so that the diagnosis of esophageal involvement is based on fluoroscopic findings during a barium meal. Esophageal involvement was present at the time of diagnosis in 64.5 per cent of those examined fluoroscopically. Studies of pulmonary function were not carried out on most of these patients; pulmonary involvement, occurring in 21.0 per cent, was determined, therefore, by the roentgenogram. The commonest finding was linear fibrosis in both bases, although some of the roentgenograms showed evidence of diffuse fibrosis and others demonstrated patchy, nodular fibrosis. Cardiac involvement was not easy to assess, the diagnosis being made in most cases on a combination of clinical and laboratory evidence, such as congestive heart failure without other cause, low voltage on the electrocardiogram, and evidence of decreased cardiac pulsation on fluoroscopy. Renal involvement

Table 3

Involvement and Complications at Time of Diagnosis of Systemic Scleroderma in 271 Patients

Involvement or complication	Number	Per cent
Cutaneous:		
Trophic changes	108	39.9
Hyperpigmentation	122	45.0
Calcinosis cutis	27	10.0
Amputation of digit	4	1.5
Visceral:		
Esophagus	136	64.5*
Lungs	57	21.0
Heart	27	8.9
Kidneys	4	1.5
Stomach†	7	—
Duodenum†	2	—
Small bowel†	4	—
Miscellaneous:		
Periodontal membrane	49	36.0‡
Hypertension	10	3.7

*Based on 211 patients who had fluoroscopic examinations.

†Barium studies were made infrequently and only when they were indicated by symptoms.

‡Based on 136 patients who had dental x-rays.

was even more difficult to evaluate and was based on the following criteria: elevation of blood urea and albuminuria with or without microhematuria, cylindruria, and hypertension. Renal involvement was found in only 4 cases. Surprisingly few patients had demonstrable evidence of involvement of the gastrointestinal tract below the esophagus, but roentgenographic examinations of the small bowel and colon were done only when symptoms were present. No instances of involvement of the colon or steatorrhea were found; this again reflects the paucity of symptoms referable to the lower part of the gastrointestinal tract. Sclerodermatous thickening of the periodontal membrane was described by Stafne and Austin[6] and was detected by widening of the periodontal space on roentgenograms. Only 10 patients were hypertensive (blood pressure of more than 160 mm. Hg systolic and 100 mm. diastolic). Included were 2 of the 4 patients with renal involvement. Most patients had low normal blood pressure.

Anemia was considered to be present if the concentration of hemoglobin was less than 11 Gm. per 100 ml. of blood in women or 12 Gm in men. Only 30 patients (11.1 per cent) were anemic by these criteria, and the anemia was usually mild. The sedimentation rate of erythrocytes was measured in 223 patients and was more than 20 mm. in 1 hour (Westergren) in 165 (73.9 per cent); 68 (30.5 per cent) had sedimentation rates of more than 50 mm. in 1 hour, and 9 had rates of 100 mm. or more. These findings were not necessarily related to other complications such as gangrene or infected cutaneous ulcers in which an elevation might be expected.

All possible combinations of degree and extent of involvement of the skin were encountered. Although the diagnosis of generalized progressive scleroderma was made not infrequently, the typical clinical pattern of this disease as described by O'Leary and Waisman was only rarely observed.

Follow-up Information

Letters of inquiry were sent to the patients who had not been examined at the Mayo Clinic since 1957. They were asked to answer a questionnaire concerning their general health, ability to work, and whether the process seemed to them to be worse, better, or the same. Follow-up information for periods of at least 5 years from time of diagnosis or until death was obtained in 236 cases (87.1 per cent). One hundred fifteen (48.7 per cent) of these patients were dead and 121 (51.3 per cent) were living.

The duration of follow-up for the 121 living patients varied from a minimum of 5 years for 7 to a maximum of 13 years for 6 patients, the average being 103.8 months from the time of original diagnosis. Forty-two patients stated that they were improved since the diagnosis was first made, 43 were worse, and 36 were about the same. These data are difficult to evaluate, since they usually represent the subjective impression by the patient. The average interval between diagnosis and death of the 115 patients who died was 41.2 months. The average age at time of death was 48.3 years; that of the men was somewhat greater than that for women (table 4).

Table 4

Age at Time of Death of 115 Patients with Systemic Scleroderma

Age, years	Women		Men	
	Number	Per cent	Number	Per cent
0 — 20	1	1.2	0	0
21 — 30	8	9.5	4	12.9
31 — 40	22	26.2	3	9.7
41 — 50	18	21.4	7	22.6
51 — 60	19	22.6	9	29.0
61 or more	16	19.1	8	25.8
Total	84	100.0	31	100.0
Average age	47.1 years		51.6 years	
Both sexes	48.3 years			

An attempt was made to ascertain the specific causes of death in these 115 patients by corresponding with family physicians, local hospitals, or relatives when death did not occur while the patient was at the clinic. Scleroderma was responsible for death in 65 of the 83 patients for whom such information was available (table 5). This was confirmed by postmortem examination in 17 cases. Congestive heart failure, pneumonia, and fulminating renal insufficiency with hypertension were the most frequent terminal events among patients who died of scleroderma.

The case records were studied to uncover any factors in the clinical course of prognostic value. The findings for the 115 patients who died (84 women and 31 men) were compared to those for the 121 patients (88 women and 33 men) who were living and on whom follow-up information was available. The initial symptoms (table 6), the ages at time of diagnosis (table 7), the extent of involvement and complications when first seen at the clinic (table 8), and the sedimentation rates of erythrocytes (table 9) were compared for the 2 groups. Twenty-two of the dead patients (19.1 per cent) had never had Raynaud's phenomenon as compared to 25 (20.6 per cent) of the survivors. Five of the dead patients and 4 of the survivors had been hypertensive at the time of original diagnosis. Nineteen of the dead patients had been anemic by the standards described previously as compared with 7 of the surviving group.

Table 5

Causes of Death of 115 Patients with Systemic Scleroderma

Cause		Deaths
Scleroderma (verified at necropsy)		17
Terminal events:		
Congestive heart failure	6	
Pneumonia	5	
Cerebral hemorrhage	1	
Malnutrition	1	
Renal failure	1	
Uncertain	3	
Probable scleroderma (no necropsy)		48
Terminal events:		
Congestive heart failure	9	
Pneumonia	3	
Renal failure	5	
Hypertension with heart failure or cerebrovascular accident	2	
Mesenteric thrombosis	1	
Infection	1	
Uncertain	27	
Miscellaneous		18
Heart disease	6	
Malignant lesion	6	
Hepatic disease	2	
Postoperative	2	
Cerebrovascular accident	2	
Unknown		32

Of 22 patients who had minimal cutaneous involvement in sites other than the hands and fingers at the time of diagnosis, 5 died. Of 52 patients in whom the sclerodermatous process had spread rapidly to involve rather large areas of the body within 1 year after onset of symptoms, 31 died. Some of this group were considered by the consulting physicians to have "generalized progressive scleroderma" instead of acrosclerosis. In most of the cases, however, the chief distinction clinically was the accelerated course of the disease.

Discussion

Generalized scleroderma has been classified as one of the systemic collagen diseases.[7] In addition to the skin it may involve the esophagus and less often other parts of the gastrointestinal tract, lungs, heart, and kidneys. The division on a clinical basis of systemic scleroderma into acrosclerosis and generalized progressive scleroderma as proposed by O'Leary

Table 6

Initial Symptoms of Scleroderma of 121 Living Patients and 115 Patients Who Subsequently Died

Initial symptom	Living patients		Dead patients	
	Number	Per cent	Number	Per cent
Raynaud's phenomenon	40	33.0	36	31.3
Scleroderma of the hands	58	47.9	58	50.4
Scleroderma of extremities or face but not of hands	10	8.3	6	5.2
Scleroderma of trunk	3	2.5	4	3.5
Generalized joint stiffness	5	4.1	5	4.3
Trophic changes	2	1.7	3	2.6
Pigmentation	2	1.7	1	0.9
Dysphagia	1	0.8	1	0.9
Dyspnea	0	—	1	0.9
Total	121	100.0	115	100.0

and Waisman[1] has not been readily accepted by other authors.[8–12]

Early symptoms of generalized scleroderma in reported series frequently include swelling and stiffness of the hands and Raynaud's phenomenon. The latter may be present for some time without other evidence of scleroderma. Orabona and Albano[13] emphasized the presence of low-grade intermittent fever as an early finding and also described a spruelike syndrome. Neither was observed in our series. Three clinical phases are described frequently: edematous phase, indurative phase, and atrophic phase. In our experience the clinical course was not so well defined as this classification would indicate.

In recent years many reports have dealt with the various systemic manifestations of scleroderma[14–22] and various aspects of cardiac,[23–25] pulmonary,[26–28] renal,[29–31] and gastrointestinal involvement[32–37] have been covered, emphasizing the protean aspects of this disease.

The course of the disease has been considered to be variable and marked by remissions and exacerbations. In a study of more than 150 cases, Leinwand and co-workers[12] in 1954 said that the disease followed no specific course, but complete resolution was rare. They

Table 7

Age at Time of Diagnosis of Scleroderma of 121 Living Patients and 115 Patients Who Subsequently Died

Age, years	Living patients		Dead patients	
	Number	Per cent	Number	Per cent
0 — 20	7	5.8	3	2.6
21 — 30	21	17.3	15	13.0
31 — 40	38	31.4	23	20.0
41 — 50	22	18.2	31	27.0
51 — 60	29	24.0	29	25.2
61 or more	4	3.3	14	12.2
Total	121	100.0	115	100.0

emphasized that dyspnea and renal involvement with hypertension were bad prognostic signs and thought that Raynaud's phenomenon made no difference in prognosis. Of their 150 patients, 22 were dead but length of follow-up was not given. Orabona and Albano[13] said that the disease progressed in waves and that the onset of visceral involvement was a bad sign with death occurring "in some years." The duration of the disease was shorter in women in their group, and they listed the major causes of death as congestive heart failure, renal insufficiency, and pulmonary insufficiency. Talbott and Ferrandis[38] also discussed the variable course and stated, "The disease may persevere for a decade or longer" or the patient may die in less than a year. Patients dying rapidly, in their experience, did so of cardiac or renal failure, and those who lived longer generally died of pulmonary complications or malnutrition. Beigelman and associates[11] reviewed 15 cases of scleroderma in which 5 deaths occurred. They agreed that Raynaud's phenomenon was of no prognostic significance. Rothman and Walker[10] stated, "The course in most cases is eminently chronic and extends over a period of many years." Piper and Helwig[39] reviewed the case material from 31 necropsies from the Armed Forces Institute of Pathology in 1955 and were unable to find any correlation between symptoms and prognosis. Seventeen of their patients had Raynaud's phenomenon, but only 5 had it as the first symptom. They stated that the earliest symptoms were referable to the joints and

Table 8

Involvement and Complications at Time of Diagnosis of Scleroderma of 121 Living Patients and 115 Patients Who Subsequently Died

Involvement or complication	Living patients		Dead patients	
	Number	Per cent	Number	Per cent
Cutaneous:				
Trophic changes	46	38.0	45	39.1
Hyperpigmentation	50	41.3	62	53.9
Calcinosis cutis	11	9.1	11	9.6
Amputation of digit	2	1.7	2	1.7
Visceral:				
Esophagus	56	59.6*	63	69.2†
Lungs	24	19.8	24	20.9
Heart	7	5.8	16	13.9
Kidneys	0	—	4	3.5
Stomach‡	5	—	1	—
Duodenum‡	1	—	1	—
Small bowel‡	1	—	2	—
Miscellaneous:				
Periodontal membrane	22	34.9§	21	38.2¶
Hypertension	4	3.3	5	4.3

*Based on 94 patients who had fluoroscopic examinations of esophagus.

†Based on 91 patients who had fluoroscopic examinations of esophagus.

‡Barium studies were made infrequently and only when indicated by symptoms.

§Based on 63 patients who had dental x-rays.

¶Based on 55 patients who had dental x-rays.

were followed by skin changes. They thought too that patients who had Raynaud's phenomenon had visceral involvement earlier than those who did not have Raynaud's phenomenon. Pathologically they found involvement of the skin in all 31 cases, cardiac and pulmonary involvement in 90 per cent, renal in 74 per cent, and gastrointestinal involvement in 64 per cent. They reviewed the postmortem findings in 27 cases of circumscribed scleroderma and found no visceral involvement.

Our study of 271 patients indicates that the prognosis in scleroderma is not so favorable as is generally believed; 115 (48.7 per cent) of the 236 patients for whom follow-up information was obtained were dead. Determining the prognosis for the individual patient was difficult. The presence or absence of Raynaud's phenomenon did not seem to be related to prognosis. Likewise sex and mode of onset of

Table 9

Sedimentation Rates of Erythrocytes at Time of Diagnosis of Scleroderma for 99 Living Patients and 97 Patients Who Subsequently Died

Sedimentation rate (Westergren), mm. in 1 hour	Living patients		Dead patients	
	Number	Per cent	Number	Per cent
Less than 20	33	33.3	18	18.6
21 — 50	49	49.5	39	40.2
51 — 99	17	17.2	32	33.0
100 or more	0	—	8	8.2
Total	99	100.0	97	100.0

the disease bore no relation to the course of the disease. Pulmonary involvement as well as involvement of the periodontal membrane and presence of calcinosis and trophic changes were unreliable prognostic signs. The mortality rate was somewhat higher for those patients who had esophageal involvement or hyperpigmentation at time of diagnosis.

The most significant findings in our series of patients with regard to predicting a poor prognosis were presence of cardiac involvement, renal involvement, anemia, and erythrocyte sedimentation rate of more than 50 mm. in 1 hour (Westergren method).

The causes of death in our series generally conformed to those reported by other authors. The leading contributing cause was congestive heart failure. Pneumonia and various pulmonary complications were next most common, followed by renal failure. Several of the patients succumbed to rapidly fulminating renal failure associated with malignant hypertension.

Finally, it is apparent from this study that the classification of systemic scleroderma into acrosclerosis and generalized progressive scleroderma is an artificial one and has no clinical or prognostic value.

Although the prognosis is better for patients with slowly progressing disease and minimal cutaneous involvement in sites other than the hands than for those with fulminating disease in which the sclerodermatous process spreads rapidly to involve large cutaneous areas of the body, one is hardly justified in separating these two extremes into separate entities on this basis alone. In most cases the course of the disease does not fall into either of these two

categories. Since the rapidity of progression of the disease seems to be the only distinguishing feature, it would be less confusing to designate systemic scleroderma as acute, subacute, or chronic and to omit other types of classification.

Summary

Two hundred seventy-one patients with unequivocal systemic scleroderma for whom the diagnosis was first established at the Mayo Clinic between January 1, 1945, and December 31, 1952, have been studied. Follow-up information was obtained 5 to 13 years after the diagnosis at the clinic concerning 236 of these patients, 115 of whom were dead. The cases were analyzed in an effort to determine what factors had a bearing on prognosis. The following seemed to bear little relation to the ultimate prognosis: sex, mode of onset, Raynaud's phenomenon, involvement of lungs and periodontal membrane, calcinosis cutis, and trophic changes. The following were considered poor prognostic omens: cardiac or renal involvement, significant elevation of the erythrocyte sedimentation rate, and anemia.

The prognosis in systemic scleroderma was found to be worse than previous reports had indicated. This study yielded no basis for the subdivision of systemic scleroderma into acrosclerosis and generalized progressive scleroderma.

Summario in Interlingua

Esseva studiate le casos de 271 patientes con scleroderma systemic inequivoc in qui le diagnose esseva primo establite al Clinica Mayo inter le 1 de januario 1945 e le 31 de decembre 1952. Information de controlo sequential esseva obtenite inter 5 e 13 annos post le diagnose in le casos de 236 de ille patientes. Cento dece-cinque habeva morite. Le casuistica esseva analysate pro determinar qual factores esseva de importantia pro le prognose. Pareva esser pauco relationate al ultime resultato: sexo, modo de declaration, phenomeno de Raynaud, affection del pulmon e del membrana periodontal, calcinosis del pelle, e alterationes trophic. Esseva de mal auguro: affection cardiac o renal, acceleration significative del sedimentation erythrocytic, e anemia.

Esseva trovate que le prognose in scleroderma systemic es pejor que lo que esseva indicate in previe reportos. Le studio forniva nulle base pro le subdivision de scleroderma systemic in acrosclerosis e generalisate scleroderma progressive.

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On Cardiac Murmurs

By Austin Flint, M.D.

The mitral direct murmur is produced by the mitral direct current of blood forced by the auricular contractions through a contracted or roughened mitral orifice. Hence, the facts just stated with regard to the current, apply to the murmur. The murmur occurs just before the ventricular systole or the first sound of the heart; it continues up to the occurrence of the first sound, and instantly ceases when the first sound is heard. It is not strictly correct to call this a diastolic murmur; it does not accompany the second or diastolic sound of the heart.—*Am. J. M. Sc.* n.s. 44: 29, 1862.

Cardiovascular Manifestations in Argemone Mexicana Poisoning (Epidemic Dropsy)

By L. M. Sanghvi, M.R.C.P. (Lond.), D.T.M.&H. (Eng.), S. N. Misra, M.D., and T. K. Bose, M.D.

THE SYNDROME of epidemic dropsy is characterized by edema, its other chief manifestations being diarrhea, pyrexia, anemia, dyspnea, tachycardia, and elevated erythrocyte sedimentation rate. It was earlier believed to be a toxic syndrome caused by ingestion of poisonous bases formed in rice under certain conditions.[1] That the disease is due to argemone poisoning has since been shown by the finding of argemone oil contamination in ingested mustard oil[2, 3] and experimental production of the disease in animals and human beings by administration of argemone oil.[4–7] While outbreaks, some of them with a high incidence of mortality, have been reported mostly from India, the disease has also been reported from Fiji, Burma, and Africa.[8–12] Mustard oil expressed from mustard seeds is used extensively in many states in India, particularly in Bengal and Assam, as a medium for cooking or frying vegetables and other food articles in place of butter, margarine, or other edible fats used in western countries.

Acton and Chopra[13] first reported that pathologic changes in this disease are characterized by dilatation of the capillaries, and changes in the heart consist of increased vascularity, gross capillary dilatation, and edema separating the muscle fibers, which are otherwise normal. Shanks and De[14] confirmed these changes and noted that both ventricles are equally involved. Though mention was made in the earlier literature of cardiac dilatation, murmurs, and failure, cardiovascular manifestations in epidemic dropsy were first stressed by Chopra and Basu[15] and Chopra and Bose[16] and have since been described in several reports.[17–21] There has, however, been no comprehensive study, and the findings have often not been substantiated by sufficient laboratory data. The purpose of this paper is to report a study of 11 cases of argemone poisoning to focus attention on this disease and to stress that several aspects of this disease are not clearly understood and require further investigation.

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Material and Methods

Eleven patients who gave a history of ingestion of mustard or groundnut oil were selected for this study; in each instance the sample of consumed oil was proved on chemical examination to be contaminated with argemone oil. There were 8 male and 3 female patients, and their ages ranged from 11 to 40 years, with an average of 19 years. The duration of the symptoms at the time of admission varied between 6 days and 3 months, with an average of 39 days. Eight patients gave a history of edema in other members of the family. All patients were hospitalized until they were cured.

The following laboratory investigations were carried out: red blood cell, reticulocyte, and total differential leukocyte counts; hemoglobin; erythrocyte sedimentation rate (Westergren); osmotic fragility; blood sugar, urea, and free and esterified cholesterol; total proteins and albumin: globulin ratio; glucose tolerance test, serologic tests for syphilis, and liver function tests; examination of urine, stool, cerebrospinal fluid, and smear from sternal marrow; fluoroscopic examination and a posteroanterior roentgenogram of the chest; a 12-lead electrocardiogram; a ballistocardiogram with a 2-coil electromagnetic apparatus of the Dock type with a 20-mfd. condenser in circuit and attached in series with limb lead II of a direct-writing Burdick electrocardiograph; determination of the venous pressure by direct method, and of arm-to-lung and arm-to-tongue circulation times by ether and magnesium sulfate methods, respectively; liver biopsy with a Vim-Silverman needle; and cutaneous patch test with argemone oil.

Results

Edema was present in all the cases, being the initial symptom in 6 of them. It was confined to the lower extremities in 8 and was generalized in 3 cases. As a rule it either appeared or increased after exertion. It preceded dyspnea except in 2 patients who had fever and were confined to bed from the onset. Two patients were orthopneic and 4 had exertional dyspnea (table 1). Dyspnea was never an ini-

Table 1

Significant Clinical and Laboratory Data on Admission in Eleven Patients

Case no.	Age and sex	Cardiac rate	Blood pressure (mm. Hg)	Venous pressure (cm. saline)	Circulation time per seconds: Arm to tongue	Circulation time per seconds: Arm to lung	Hemoglobin (Gm./100 ml.)	Dyspnea	Roentgen: Lung congestion	Roentgen: Heart	Liver enlargement	ECG	BCG
1	11 M	120	135/70	8.2	10	4	8	—	++	RV +	++ ascites	LVHP, T, S-T	N
2	40 F	140	120/78	10.2	11	6	8.4	orthopnea	+++	PA +	+++ ascites	S-T, T	J-K slurred
3	16 F	124	106/54	14.6	14	7	6.2	orthopnea	bilateral pleural effusion	N	+++ ascites	hypokalemic pattern	J notched, J-K slurred R-V gr. I short k
4	13 M	110	140/70	11	11	5	14	—	++	RV + LV +	nil	LVHP, T, S-T	N
5	11 M	130	110/60	15.8	10	4	10.4	—	+++	N	+	LVHP, S-T	tall H
6	13 M	110	148/82	12	9	4	12	—	+	N	++	LVHP, S-T, T	N
7	25 M	92	145/70	14.4	10	4	10	exertional	nil	RV +	+	S-T	J-K slurred
8	14 M	96	138/82	14.8	8	4	12	exertional	nil	N	nil	LVHP, T, S-T	tall H, short K, slurred J-K
9	30 M	120	138/70	8.8	14	6	10	exertional	nil	RV +	++	BVHP	tall H, J-K slurred
10	27 M	94	120/70	10.4	10	5	14	—	nil	N	+	BVHP	tall H, short K
11	20 F	128	128/66	6.2	11	6	8.2	exertional	nil	N	+	S-T, T	N

Abbreviations: Plus signs indicate presence and degree; LVHP and BVHP, left and biventricular hypertrophy, respectively; RV, right ventricle; LV, left ventricle; PA, pulmonary artery; N, normal.

tial symptom but appeared after an interval of from 10 days to 2 months after the initial symptom. It improved rapidly and always disappeared before edema. Eight patients had pyrexia, which was present at the onset in 5 of them. Other manifestations included cough in 4 cases, palpitation in 2, diarrhea in 2, headache, impotence, and amenorrhea in 1, anemia in 9, ascites in 3, and lymphadenopathy in 3 cases.

The cardiac rate was rapid, and the blood pressure was normal in all cases. The pulse pressure was more than 60 in 6 cases but in none was a water-hammer pulse noted. Heart sounds were altered in all the cases; there was an apical protodiastolic gallop in 5 cases with a systolic gallop in 1, accentuation of the mitral first sound in 7, and of the pulmonic second sound in 5 cases. Gallop rhythm disappeared within a few days, with slight improvement of the disease. Murmurs were heard in 7 cases, systolic pulmonary alone in 3, systolic mitral alone in 1, systolic mitral and pulmonary in 2, and systolic and presystolic mitral in 1 case.

Roentgen examination showed cardiac enlargement in 4 cases: the right ventricle was enlarged in all 4 and the left ventricle in 1. The enlargement was slight, the maximum cardiothoracic ratio being 50 per cent, and was confirmed when subsequent examination revealed reduction in size. There was prominence of vascular markings in all 11 cases, with pulmonary congestion in 5 of them. The liver was enlarged in 9 cases.

The venous pressure was elevated in 4 cases. The circulation time was considered prolonged in 1 case in which the hemoglobin level was 6.2 Gm. per 100 ml.

The electrocardiogram was abnormal in all cases, and abnormalities consisted of S-T changes in 9 cases, T changes in 6, pattern of left ventricular hypertrophy in 5, biventricular hypertrophy pattern in 2, and hypokalemic pattern in 1 case. The criteria of Sokolow and Lyon[22, 23] were used to determine patterns of ventricular hypertrophy. The ballistocardiogram was abnormal in 7 cases; the abnormalities consisted of tall H in 4 cases, short K in 3, slurred J-K in 5, and notched J in 1 case (figs. 1 and 2).

There was leukocytosis in 2 cases, but no eosinophilia was observed. Anemia was present in 9 cases; the bone marrow smear showed normoblastic reaction in all 9 and late normoblastic reactions in 3 of them. In the absence of reticulocytes or normoblasts in the peripheral blood the anemia appeared to be due to a maturation defect in the bone marrow. The sedimentation rate was raised in 10 cases. Cutaneous patch test to determine allergy to argemone oil was negative in all cases. The total blood proteins were diminished in 3 cases, and the albumin:globulin ratio was deranged in these 3 and in 4 other cases with increase in the globulin fraction. Blood cholesterol was elevated in 7 cases. Liver function tests were abnormal in 3 cases. The urine, the cerebrospinal fluid, the blood urea and sugar, and the glucose tolerance test were normal, and the serologic tests for syphilis were negative in all cases. The changes seen in liver biopsy included cloudy swelling, reticuloendothelial-cell hyperplasia, congestion of the central vein, distention of the sinusoids, and scanty hemorrhages.

The usual sequence of disappearance of the manifestations was dyspnea, gallop rhythm, pulmonary congestion, edema, tachycardia, enlarged liver, elevated sedimentation rate, anemia, and murmurs.

Discussion

Chopra and Bose[16] noted that while cardiac involvement was the rule in epidemic dropsy, its severity was not uniform. They described 3 types of cardiovascular manifestations, the acute fulminating and fatal type resembling acute left ventricular failure, the subacute or the chronic type, and formes frustes with slight or no cardiac involvement. Congestive cardiac failure has been described by several writers, and acute cardiac failure and acute dilatation of the heart have been reported to be the cause of death in this disease.[15, 16, 18-21, 24]

In the present series, the onset was insidious and the progress slow in all the cases. The prominent manifestations were edema, dysp-

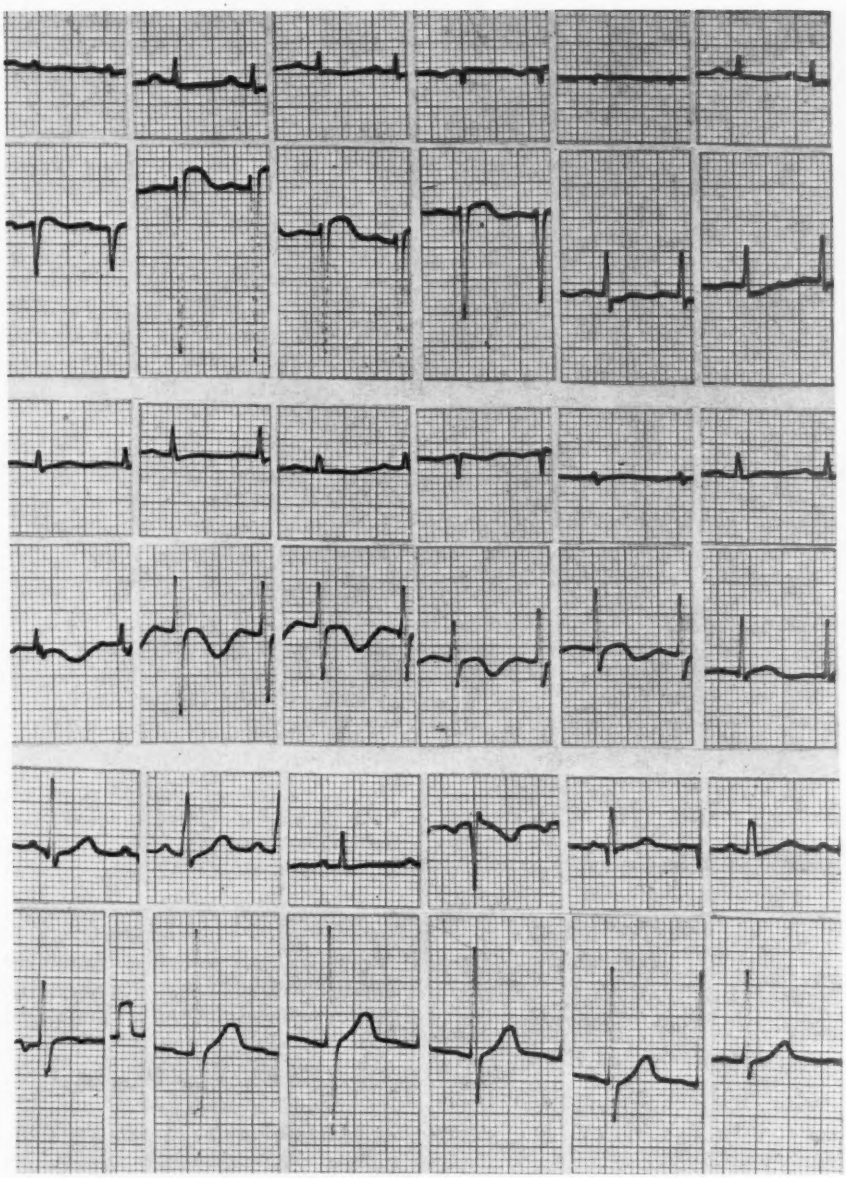

Figure 1

Electrocardiograms: Case 2 (top) *shows S-T and T changes. Case 3* (middle) *shows hypokalemic pattern. Case 9* (bottom) *shows biventricular hypertrophy pattern 0.5 mm. voltage in V_2 to V_6.*

ea, pulmonary congestion, and hepatic enlargement. Edema was not related to the erum protein level and the albumin:globulin atio or to the hemoglobin level. It was not associated with elevated venous pressure in 7 cases, including 2 of the 3 cases with generalized anasarca. The venous pressure was normal in 6 of the 9 cases with hepatic enlarge-

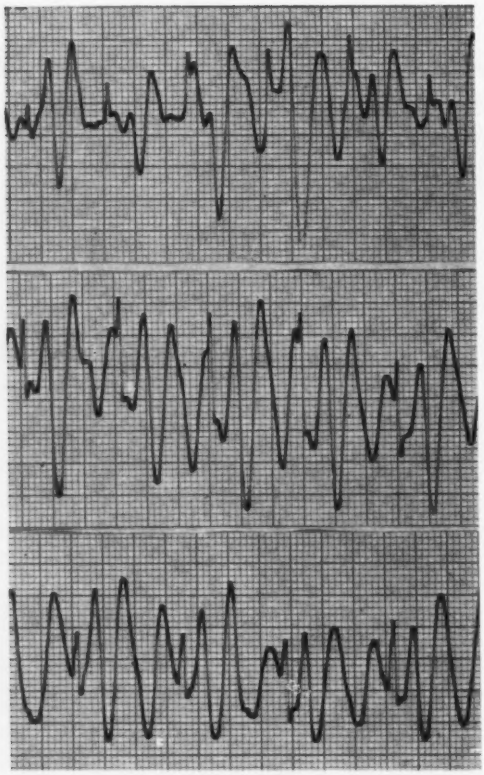

Figure 2

Ballistocardiograms: Case 3 (top) *shows notched J, slurred and notched J-K, short K, and grade-I respiratory variation. Case 8* (middle) *shows tall H, short K, and slurred J-K. Case 9* (bottom) *shows tall H and slurred J-K.*

ment, including 2 of the 3 cases with considerable enlargement. The circulation time was normal in 10 cases. Edema and hepatic enlargement therefore could not be attributed to congestive failure in most of the cases. Moderate to severe pulmonary congestion was demonstrated roentgenologically in 5 cases. It did not appear to have definite relation to cardiac enlargement; in cases 2 and 5, with severe congestion, there was no demonstrable cardiac enlargement. It is realized that cardiac enlargement may not be demonstrable in some cases of left ventricular failure. Congestion was, however, not associated with a prolonged circulation time in any of the 5 cases, and in 4 of them there was no dyspnea. It therefore appeared unlikely that left heart failure was responsible for pulmonary congestion. Capillary dilatation has been reported to be the characteristic pathologic change in epidemic dropsy, and it is conceivable that it plays a major role in the causation of edema, hepatomegaly, and pulmonary congestion.

Chopra and Bose[16] noted that dyspnea may occur early in epidemic dropsy while there are no gross changes in the cardiovascular or respiratory systems. They suggested 4 possible causes of dyspnea: (1) toxins acting on the respiratory center; (2) turgid lung capillaries encroaching upon the alveolar spaces; (3) anemia of the respiratory center; and (4) cardiac failure. In the present series in cases 2 and 3 with orthopnea the roentgen examination showed bilateral pleural effusion in one and severe pulmonary congestion in the other. In the former the circulation time was considered prolonged, the venous pressure was elevated, and the dyspnea could be attributed to cardiac failure, whereas in the latter it could be attributed to pulmonary congestion. It is conceivable that in these 2 cases and in case 11 anemia may have been partly responsible for dyspnea because the hemoglobin was less than 9 Gm. per 100 ml. There was, however, no definite relation between dyspnea and pulmonary congestion because in none of the 4 patients with exertional dyspnea was there roentgen evidence of congestion, and in 4 of the 5 patients with congestion there was no dyspnea. As stated earlier, heart failure was considered unlikely in 5 of the 6 cases with dyspnea. The mechanism of dyspnea was thus not clearly understood.

In this series cardiac enlargement was minimal and was mostly right ventricular in type, while in other reports left ventricular enlargement has been described as common.[15, 18] Except in one case with hypokalemia, the electrocardiographic and the ballistocardiographic changes were also minor. The former, apart from the nonspecific S-T and T changes, were characterized by a hypertrophy pattern, predominantly of the left ventricular type. Shortening of the P-R interval[17] was not found in any case on comparison with the

tracings taken after cure. The short K wave in the ballistocardiogram was not related to lowered peripheral resistance; there was no lowering of the diastolic pressure in any case with this abnormality, and this abnormality was not present in the only case with lowered diastolic pressure. The abnormalities may be due to inefficient myocardial ejection.[25]

It was thus seen that while tachycardia, alterations in the heart sounds, cardiac enlargement, or the electrocardiographic and ballistocardiographic changes indicated myocardial involvement in every case in this series, the latter appeared to be of a minor nature. The findings may be attributed to a nonspecific type of myocarditis, a term which includes not only inflammatory and specific lesions but degenerative and other lesions encountered in a variety of other conditions.[26] In some of our cases dyspnea or orthopnea and clinical and roentgenologic evidence of severe pulmonary congestion simulated left ventricular failure, and these findings associated with edema, and enlarged tender liver simulated congestive cardiac failure. It was therefore of interest that the presence of cardiac failure was considered unequivocal in one case only. In others it was considered unlikely, or at least it was not a dominant feature. Congestive cardiac failure occurs only occasionally as a result of myocarditis alone, except in rheumatic fever.[27]

It is thought that the clinical picture in argemone poisoning may be misleading and heart failure may be diagnosed incorrectly in the absence of laboratory data, and that congestive failure is unlikely to be the cause of death in argemone poisoning. The characteristic pathologic change in this disease is vascular dilatation, and it seems more likely that the fatal termination, which occurs with extreme rapidity, is due to acute circulatory failure or shock as a result of severe vasodilatation with consequent pooling of the blood in the small vessels. It must also be emphasized that the clinical picture in argemone poisoning may lead to an erroneous diagnosis of rheumatic heart disease (case 1) and even miliary tuberculosis (case 2).

The chemical nature of the toxic substance in argemone oil (derived from the seeds of the plant argemone mexicana) is uncertain. Mukherjee and co-workers[28] isolated a crystalline free base C_{19} H_{15} O_4 N from the oil and suggested that this represented the toxic fraction. Sarkar[29] found that the oil contained at least 2 toxic alkaloids, dihydrosanguinarine and sanguinarine, forming 87 and 5 per cent, respectively, of the total alkaloids, the latter being more toxic. Mitra[30] however observed that even that fraction of the oil from which the above 2 alkaloids were removed was toxic. It has also been observed that toxicity of different batches of argemone oil varies,[31] and 2 different toxic alkaloids, argemonine (protopine) and berberine, have been found in the African plant.[11]

Treatment of argemone poisoning has also remained a problem. Chopra and Basu[15] found digitalis ineffective and sometimes even harmful, while Chaudhuri and Chakravarty[19] suggested that it should be tried in all cases with heart failure. The latter authors noted dramatic response, even of heart failure, to Phenergan. Administration of rutin and vitamins C, D, and P, for protection and restoration of damaged capillaries, and of a diet rich in protein and poor in fat with glucose, and insulin and vitamin B complex, for protection of the liver, have been recommended.[11] In one instance dramatic improvement was noted after cortisone therapy.[32] In animal experiments, however, rutin, Phenergan, ephedrine, BAL, cortisone, and BAL with cortisone were found to possess no effect in preventing the toxic effects of argemone oil.[33] In this study digitalis, administered in cases with orthopnea or severe pulmonary congestion, and antihistaminics were found to be of no value. Antianemic drugs including iron preparations, liver extract, folic acid, and cyanocobalamine were found ineffective for some time, probably because of depression of the bone marrow. For the present, early recognition of the condition and immediate stoppage of the incriminating oil, bed rest, and blood transfusion in cases with anemia, remain the main principles of treatment in chronic cases. In

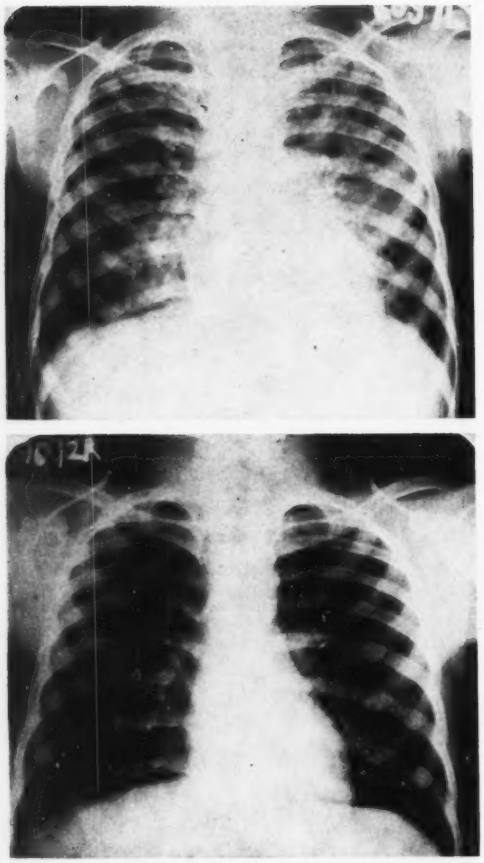

Figure 3

Roentgenograms of case 1. Top. *On admission, September 19, 1957; shows slight cardiac enlargement with straight left border and pulmonary congestion, more marked on left side.* Bottom. *November 27; normal heart and lung fields.*

cases with acute circulatory failure (not encountered by us) measures to combat shock should prove beneficial.

Case Reports

Case 1

An 11-year-old boy was admitted on September 19, 1957, complaining of cough for 2 months, intermittent fever and edema of the feet for 6 weeks, oliguria for 15 days, and edema of the face for 3 days. There was no history of diarrhea and dyspnea.

Examination revealed generalized anasarca, slight ascites, cardiac rate of 120 per minute, blood pressure 135/70, and liver enlarged 2½ inches below the costal margin and tender. There was a presystolic murmur at the mitral area, and the pulmonary second sound was accentuated.

Laboratory examination of the blood revealed hemoglobin, 8 Gm. per 100 ml.; erythrocyte sedimentation rate, 42 mm. per hr.; cholesterol, 350 mg. per cent; and total proteins 4.38 Gm. per cent, with an albumin:globulin ratio of 1.1:1. The venous pressure was 8.2 cm. of saline, and the arm-to-tongue and the arm-to-lung circulation times were 10 and 4 seconds, respectively. A roentgenogram of the chest (fig. 3) showed prominent vascular shadows, moderate pulmonary congestion, and slight enlargement of the cardiac shadow with straight left border. Fluoroscopy showed right ventricular enlargement. The electrocardiogram showed left ventricular hypertrophy and S-T and T changes, and the ballistocardiogram was normal.

On October 2 the cardiac rate had decreased to 97 per minute, the edema had diminished, and the presystolic murmur had disappeared. Roentgenogram on October 5 showed absence of pulmonary congestion, while the cardiac shadow was still enlarged. On October 20, edema had disappeared and the blood pressure had decreased to 110/60. On November 16, the pulse rate was 72 per minute, the systolic murmur had disappeared, the erythrocyte sedimentation rate had decreased to 17 mm. per hour, the hemoglobin was 12.5 Gm. per 100 ml., and the liver had receded below the costal margin. Roentgenogram on November 27 showed a normal-sized heart (fig. 3).

Comment

At the time of admission a diagnosis of rheumatic mitral stenosis with congestive heart failure was made in this case because of the elevated erythrocyte sedimentation rate, mitral presystolic murmur, pulmonary congestion, and cardiac configuration. The presystolic murmur was not considered to be due to anemia as it is not encountered when the hemoglobin level is 8 Gm. per 100 ml.[34] Absence of dyspnea and normal venous pressure and circulation time were, however, evidences against congestive failure. History of ingestion of groundnut oil and of edema in other family members, and disappearance of the murmur after improvement established the diagnosis of argemone poisoning.

Case 2

A 40-year-old housewife was admitted on October 12, 1957, complaining of irregular pyrexia for 2 months, weakness, palpitation, and dyspnea on exertion for 1 month, edema of the feet for 15 days, orthopnea for 8 days, and dry cough for 4 days.

Examination revealed a moderately anemic woman in severe distress with orthopnea, edema of

the feet and face, slight enlargement of cervical and axillary lymph nodes, temperature of 100 F., cardiac rate of 140, respiratory rate of 38 per minute, a blood pressure of 120/78, a tender liver enlarged 3 inches below the costal margin, and slight ascites. There was no cyanosis or engorgement of the neck veins. The cardiac borders appeared to be enlarged clinically, the mitral first sound and the pulmonic second sound were accentuated, and there was a protodiastolic apical gallop. Rales were heard over both lungs.

Laboratory examination revealed hemoglobin, 8.4 Gm. per 100 ml.; erythrocyte sedimentation rate, 43 mm. per hour; blood cholesterol, 290 mg. per cent; blood proteins, 5.4 Gm. per cent, with an albumin-globulin ratio of 1.8:1, venous pressure, 10.2 cm. of normal saline; and arm-to-tongue and arm-to-lung circulation times, 11 and 6 seconds, respectively. A roentgenogram of the chest (fig. 4) showed a normal-sized heart, prominent pulmonary artery and vascular shadows, and extensive mottling over both the lung fields. The electrocardiogram showed S-T and T changes, and the ballistocardiogram showed slurred J-K segment. The liver biopsy showed congestion of the central veins, cloudy swelling of the cells, and reticuloendothelial-cell hyperplasia. Biopsy of an axillary lymph node showed reactive hyperplasia.

The patient was given 1 mg. of strophanthin intravenously followed by Digoxin, 1 tablet every 8 hours orally, but with no significant influence on dyspnea and heart rate. The condition gradually improved and the temperature returned to normal on October 17; the heart rate was still 116 per minute. Digoxin was then discontinued. By October 21 there was no orthopnea, edema, or ascites, and the patient had lost 8 pounds of weight. The gallop rhythm was not audible, but a systolic murmur was heard at the mitral and the pulmonic areas. Roentgenogram of the chest showed some pulmonary congestion on November 7 and was normal on November 25 (fig. 4). The hemoglobin, the erythrocyte sedimentation rate, and the liver returned to normal only after 3½ months of treatment.

Comment

In this case, at the time of admission, orthopnea, severe pulmonary congestion, enlarged tender liver and the electrocardiographic changes suggested a diagnosis of myocarditis with severe cardiac failure. The normal-sized heart and normal venous pressure and circulation times, however, were evidences against failure. Miliary tuberculosis with secondary anemia and edema due to hypoproteinemia was also considered because of irregular pyrexia, lymphadenopathy, and the chest roentgenogram. The blood examination, however, revealed normal proteins, the lymph node biopsy did not show tuberculous lesion, and the temperature settled to normal 5 days after admission without antibiotic therapy. History of use of mustard oil, which was proved to contain argemone oil, and of edema in other members of the family established the diagnosis.

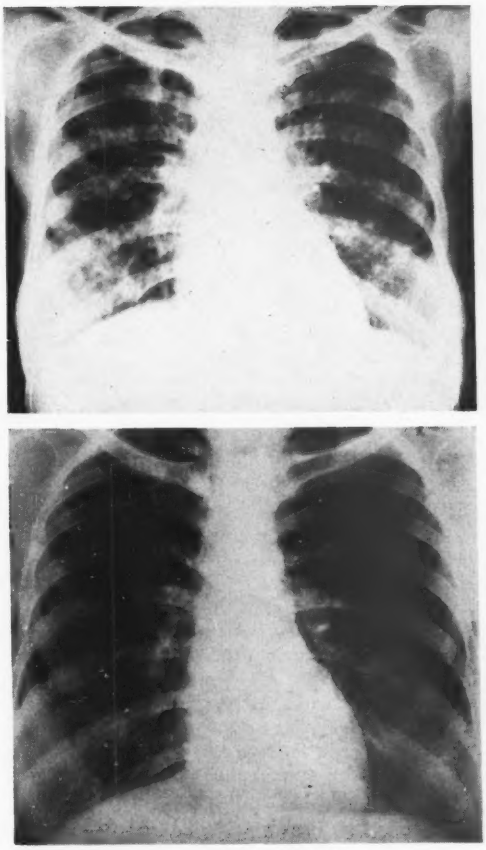

Figure 4

Roentgenograms of case 2. Top. *On admission, October 12, 1957; prominent pulmonary artery, severe pulmonary congestion, and normal-sized heart.* Bottom. *November 25; normal heart and lung fields.*

Case 3

A 16-year-old girl was admitted on November 9, 1957, complaining of irregular pyrexia for 3 months, anorexia, cough, and diarrhea with 6 to 8 stools per day for 2 months, dyspnea on exertion for 1 month, edema of the feet for 15 days, and orthopnea for 8 days. She had amenorrhea for 3 months.

Examination revealed a well-built and poorly

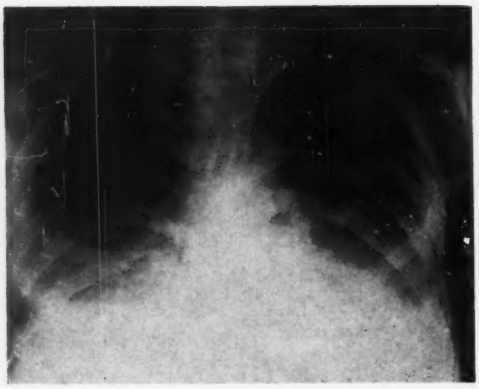

Figure 5

Roentgenogram of case 3 showing bilateral pleural effusion.

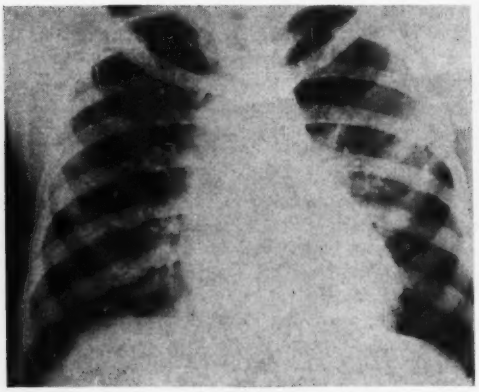

Figure 6

Roentgenogram of case 4 showing cardiac enlargement and pulmonary congestion, more marked on left side.

nourished girl with orthopnea, edema of the feet, severe anemia, cardiac rate 124 and respirations 36 per minute, temperature 100.4 F., blood pressure 106/54, liver enlarged 3 inches below the costal margin, and slight ascites. The neck veins were slightly engorged. There were systolic and proto-diastolic gallop sounds at the mitral area and signs of moderate pleural effusion on both sides.

Laboratory examination revealed hemoglobin, 6.2 Gm. per 100 ml.; erythrocyte sedimentation rate, 11 mm. per hour; total leukocyte count 16,200 per mm.,^{3} with a normal differential count; proteins, 3.61 Gm. per cent, with an albumin : globulin ratio of 1.1 :1; cholesterol, 235 mg. per cent; venous pressure, 14.6 cm.; and arm-to-tongue and arm-to-lung circulation times, 14 and 7 seconds, respectively. Roentgenogram of the chest (fig. 5) showed bilateral pleural effusion. An electrocardiogram showed changes consistent with a hypokalemic pattern, and a ballistocardiogram showed grade-I respiratory variation, notched J wave, slurred and notched J-K segment, and short K wave. The serum potassium on the same day was 3.2 mEq. per liter. The liver biopsy showed areas of parenchymal degeneration and few hemorrhages. On paracentesis, 870 ml. of clear fluid could be aspirated from the left pleural space and 900 ml. from the right, with relief of the orthopnea. The fluid was straw colored, with a protein content of 3.5 Gm. per cent and cell count of 2,200 per mm.^{3} with 95 per cent lymphocytes.

Potassium chloride was given orally in doses of 1 Gm. every 6 hours. There was considerable improvement of the electrocardiographic pattern on November 17, when potassium chloride was discontinued. The pyrexia and diarrhea subsided, and the gallop rhythm disappeared within a week. On November 17 there was no edema. On November 23 the chest roentgenogram was normal. She was discharged at request on December 5, 1957, although the hemoglobin had risen only to 10 Gm. per 100 ml.

Comment

Severe anemia with congestive heart failure due to chronic diarrhea was suspected in this case at the time of admission. Slightly elevated venous pressure, and arm-to-tongue circulation time of 14 seconds in the presence of severe anemia, were indicative of congestive failure. The high cell count in the pleural fluid was suggestive of increased capillary permeability and against a transudate due to congestive failure or hypoproteinemia. Argemone poisoning was suspected when a history of edema in other members of the family was obtained and was proved when the mustard oil consumed by the patient was found positive for argemone oil. The hypokalemia in this case was apparently due to diarrhea of 2 months' duration.

Case 4

A 13-year-old boy was admitted on January 16, 1958, complaining of edema of the feet on exertion for 6 days. There was no history of pyrexia, diarrhea, or dyspnea.

Examination revealed a well-built and well-nourished boy with 1+ edema of the feet, cardiac rate 110, and blood pressure 140/70. The heart boundary was slightly enlarged, and the mitral first sound was accentuated.

Examination of blood revealed hemoglobin, 14 Gm. per 100 ml. and sedimentation rate, 44 mm. per hour. The venous pressure was 11 cm. and the arm-to-tongue and arm-to-lung circulation times were 11 and 5 seconds, respectively. A roentgen examination (fig. 6) showed prominent

vascular shadows, pulmonary congestion more marked on the left side, and enlargement of both the ventricles. The electrocardiogram revealed left ventricular hypertrophy pattern and S-T and T changes. The ballistocardiogram was normal.

Comment

While in case 2 there were severe pulmonary congestion, orthopnea, and normal-sized heart, in this case there were cardiac enlargement and moderate pulmonary congestion, but no dyspnea.

Case 5

An 11-year-old boy was admitted on February 13, 1958, complaining of headache for 25 days, and edema of the feet and face for 15 days. There was no history of diarrhea, fever, or dyspnea.

Examination revealed a well-built, well-nourished boy with 1+ edema of the feet, cardiac rate 130, blood pressure 110/60, and just palpable liver. Mitral first sound was accentuated and there was a soft systolic murmur at the pulmonary area. Rales were heard over both lungs.

Laboratory examination revealed hemoglobin, 10.4 Gm. per 100 ml.; erythrocyte sedimentation rate 70 mm. per hour; venous pressure, 15.8 cm.; and arm-to-tongue and arm-to-lung circulation times 10 and 4 seconds, respectively. Roentgen examination (fig. 7) showed normal-sized heart, prominent vascular shadows, and severe pulmonary congestion. The electrocardiogram showed left ventricular hypertrophy and S-T changes, and the ballistocardiogram showed tall H waves.

Comment

In this patient though the venous pressure was slightly raised and there was severe pulmonary congestion, the circulation time and the heart size were normal, and, despite severe pulmonary congestion, this patient denied a history of dyspnea. The presence of cardiac failure was therefore considered unlikely.

Summary

Cardiovascular manifestations have been studied in 11 patients with argemone oil poisoning.

Tachycardia, alterations in the heart sounds, cardiac enlargement, or electrocardiographic and ballistocardiographic changes indicated myocardial involvement in every case. The latter was suggestive of a nonspecific type of myocarditis and was considered to be of a minor nature. The prominent manifestations included dyspnea, edema, hepatic enlargement, and pulmonary congestion. The last 3 were probably due to capillary dilatation, whereas the cause of dyspnea was uncertain.

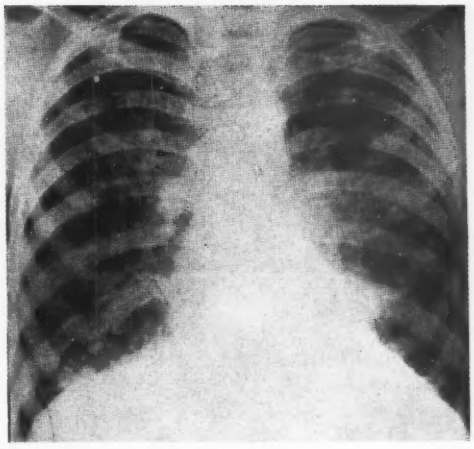

Figure 7

Roentgenogram of case 5 showing prominent vascular shadows, severe pulmonary congestion, and normal-sized heart.

These manifestations suggested the presence of cardiac failure, which, however, was considered unlikely except in 1 case.

Acknowledgment

Dr. L. R. Sarin, Superintendent, Sawai Man Singh Hospital, kindly permitted the publication of this report.

Summario in Interlingua

Le manifestationes cardiovascular esseva studiate in 11 patientes con invenenamento per oleo de Argemone Mexicana.

In omne le casos, alterationes del sonos cardiac, tachycardia, allargamento del corde, o signos electro- e ballistocardiographic reflecteva un affection myocardial. Isto pareva suggerer un typo nonspecific de myocarditis e esseva considerate como de natura minor. Le plus prominente manifestationes includeva dyspnea, edema, allargamento hepatic, e congestion pulmonar. Le ultime 3 in iste lista de manifestationes esseva probabilemente le consequentia de dilatation capillar. Le causa del dyspnea remaneva obscur.

Le complexo de manifestationes suggereva le presentia de discompensation cardiac, sed isto esseva considerate como pauco probabile, excepte in un caso.

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Impending Myocardial Infarction

Recognition and Management

By R. E. Beamish, M.D., F.R.C.P. (C), and V. Marie Storrie, M.D.

IT HAS LONG BEEN known that attacks of myocardial infarction are frequently preceded by premonitory pain. The reported incidence of such warning symptoms usually varies from 30 to 50 per cent and the fatality rate in these series has ranged from 15 to 43 per cent.

Soon after introduction of anticoagulants in the treatment of acute myocardial infarction, several authors[1-3] conjectured that this therapy might well provide a means of preventing attacks. Stimulated by the results of Wood,[1] the present study was begun in 1949. A review of this experience suggests that impending infarction can be recognized with a high degree of accuracy and that the prompt administration of anticoagulants favorably influences the outcome.

Definition and Diagnostic Considerations

Since the earliest clinical studies on myocardial infarction it has been recognized that instances are frequent in which premonitory pain foreshadows the event.[4-6]

Mounsey[6] placed the prodromal symptoms of myocardial infarction in the ill-defined borderline state between angina of effort and myocardial infarction. This state has been referred to as "coronary failure," (Blumgart et al.[7]) spontaneous "acute coronary insufficiency" (Master),[8] "intermediate coronary syndrome" (Graybiel),[9] and "slight coronary attacks" (Smith and Papp).[10] The pathologic basis of the syndrome is no doubt variable; since it commonly develops rather abruptly, it is reasonable to attribute it to coronary thrombosis, but without accompanying myocardial infarction. The outcome of the state is also variable: the patient may return to normal health, may begin or continue to have angina of effort, or may go on to myocardial infarction. The relative incidence of these 3 modes of termination is not easily obtainable in a hospital series, since few patients who do not suffer from infarction are sent to the hospital. From observations of the present study carried out in the home, office, and hospital, it is apparent that these attacks are more significant and dangerous than has been commonly realized.

Mounsey[6] found prodromal pain in 40 of 139 cases of myocardial infarction. This incidence of 29 per cent is lower than the 48 per cent and 50 per cent found by Sampson and Eliaser[11] and by Feil,[12] respectively, and higher than what Yater et al.[13] found (9.5 per cent) in men under the age of 40. Mounsey[6] suggested that the frequency is sufficient to make a recognizable clinical group. The pain was typical of cardiac ischemia in site, radiation, and quality, but differed from classical angina of effort in that there was a crescendo nature in the occurrence of symptoms, the attacks were more prolonged, and there was an inconstant relation of the pain to effort. The fatality rate in patients with prodromal symptoms was 15 per cent in Mounsey's series,[6] and 34 per cent and 43 per cent in Sampson and Eliaser's,[11] and Yater's series,[13] respectively.

Myocardial infarction may be manifest merely as angina pectoris of effort.[14] However, not infrequently myocardial infarction is preceded by an intensification of a previous angina of effort.[1, 6] The pathologic counterpart of a sudden increase in angina is frequently an occlusion of one or more major branches of the coronary arteries.[7]

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Presented in part before the Canadian Heart Association, Edmonton, Alberta, June 17, 1957, and the American College of Cardiology, Philadelphia, May 27, 1959.

In a patient who has had a previous infarct and who has been subsequently pain-free, the recurrence of pain is particularly ominous. In such patients with known coronary disease, a more or less abrupt recurrence of pain indicates a sudden increase in the occlusive disease. In this situation it is reasonable to anticipate an increased incidence of infarction.

On the basis of these considerations and from the observations of the present series, it is suggested that impending myocardial infarction has 3 common presentations:

I. Onset of ischemic cardiac pain in a patient previously free of symptoms. Usually the patient experiences repeated bouts of spontaneously occurring pain lasting from 15 to 30 minutes or longer, without clinical, electrocardiographic, or laboratory evidence of infarction. Less commonly, it may take the form of a rapidly progressive angina of effort. Whether the pain be at rest or with exertion, it occurs oftener, lasts longer, and becomes more severe over the course of a few days or weeks.

II. Intensification of angina of effort in a patient with previous angina of several months' or years' duration. Usually there is an abrupt change in the pattern of the chronic symptoms: pain occurs oftener, occurs with less provocation, lasts longer, and is more severe.

III. Recurrence of pain, at rest or on slight provocation, in a patient who has been pain-free after a previous myocardial infarction.

This classification is somewhat similar to that of Denham[15] based on study of the acute phase of myocardial infarction in 920 patients.[16]

Patients with symptoms of impending infarction are to be distinguished from those with potential recurrent infarction as described by Nichol and Fassett[17] and others.[18, 19] In this latter group, patients with previous infarction are placed on long-term anticoagulant therapy to prevent a recurrence of infarction. In group III of the present series the indication for anticoagulants was the recurrence of pain rather than the mere fact of previous infarction.

Whenever a patient is suspected of impending myocardial infarction because of ischemic pain, the electrocardiogram may provide helpful confirmatory evidence. The changes consist of primary T-wave abnormalities or S-T depressions. Such alterations are particularly helpful if electrocardiograms before the onset of pain are available for comparison. It must be stressed, however, that the clinical diagnosis must be acted upon even if the electrocardiogram is normal. Unfortunately it has been an all too common experience to have patients report to a physician because of pain, have an electrocardiogram done, be told that it is normal, be reassured, and then die suddenly a short time later. We have frequently observed that serial electrocardiograms, taken over a period of several days at the onset of treatment for impending infarction, may show transitory but conclusive evidence of ischemia. To wait for incontrovertible electrocardiographic changes is to waste precious time and may permit preventable infarction to occur.

Patients and Methods

From early 1949, all patients with symptoms of any of the 3 categories of threatened infarction were diagnosed as impending myocardial infarction and immediate hospitalization for anticoagulant treatment and rest was advised. By December, 1957, this diagnosis and recommendation had been made in 100 patients. In 85 of the 100 patients this recommendation was carried out; in the remaining 15 patients it was not. The latter patients therefore serve as "control" subjects.

All patients were seen by the same observers and the diagnoses were based on the same criteria. In some additional instances there was doubt at the onset of symptoms but treatment was started in any case. After a period of observation had enabled a diagnosis other than impending infarction to be established, such cases were eliminated from the series. Also, after some days of observation, it became apparent in a few cases that infarction had occurred at the time of presentation. These cases also were eliminated from the study. It must be constantly remembered that accurate diagnosis of impending infarction can sometimes be made only in retrospect but treatment must be initiated at the outset of a suspicious assembly of symptoms.

In the early years of the study patients were admitted to the hospital as soon as possible after diagnosis for treatment with anticoagulants. More recently, in a few cases, anticoagulants have been

administered in the office or home, pending admission to hospital. In addition to oral anticoagulants, in patients with rapid progression of symptoms, heparin was administered in a dose of 50 mg. intravenously every 4 hours until prothrombin activity reached a therapeutic level. A total of 21 patients received heparin, the remainder received only oral preparations. From 1949 to 1951 the oral anticoagulant used was bishydroxycoumarin (Dicumarol);* subsequently the usual preparation was phenylindanedione (Danilone). Later, ethyl biscoumacetate (Tromexan) and acenocoumarin (Sintrom) were also used. Among the 85 cases that received anticoagulants, Dicumarol was given to 8 patients, Sintrom to 4 patients, Tromexan to 1, and the remaining 72 were given Danilone.

After admission to the hospital, patients received a complete physical examination, a 12-lead electrocardiogram, and roentgen examination of the chest. Routine laboratory investigation included complete blood count, Kahn test, estimation of sedimentation rate, fasting blood sugar, and serum cholesterol. Electrocardiograms and sedimentation rates were repeated several times during the first few days, and subsequently as indicated by symptoms; they were again performed prior to discharge from hospital, usually 2 to 4 weeks later. Serum transaminase and other enzymes were measured in more recent cases.

Patients were encouraged to remain in bed, usually with bathroom privileges, until therapeutic anticoagulation was achieved, and until they were no longer subject to pain. They then became ambulant. When levels of prothrombin activity were stabilized in the therapeutic range patients were allowed to go home. Reexaminations were carried out at intervals of 1 to 3 months, or as clinically required.

Prothrombin activity was estimated at the onset of treatment and daily thereafter while patients were in the hospital. After discharge it was estimated at weekly, and later at 2 weekly intervals. The prothrombin activity was estimated by the 1-stage method of Quick, the normal control value being 12 to 15 seconds. The upper and lower limits of the therapeutic range were considered to be 25 to 50 seconds (35 and 17 per cent, respectively).

It soon became apparent that there was considerable advantage in securing prompt control of prothrombin time with oral anticoagulants, thus permitting earlier discontinuance of intravenous injections of heparin. With the usually recommended doses of phenylindanedione, several days were often necessary before the therapeutic range was reached. Accordingly a study[20] of optimum dosage to achieve rapid effect was undertaken. With larger doses (e.g., 500 to 600 mg. in the first 24 hours), a more rapid control could be safely effected. These larger doses were not used in patients over the age of 65 or in patients with any evidence of congestive heart failure. In the case of Tromexan, Dicumarol, and Sintrom, standard initial and maintenance doses were used.

*For simplicity, the trade-names of these compounds are used hereafter.

Table 1

Age and Sex Distribution

Age in years	Numbers of cases					
			Anticoagulant		"Control"	
	Male	Female	Male	Female	Male	Female
30—39	3	—	3	—	—	—
40—49	16	—	14	—	2	—
50—59	38	5	31	4	7	1
60—69	19	12	16	11	3	1
70 and over	6	1	5	1	1	—
Totals	82	18	69	16	13	2
	100		85		15	

Clinical Features of Patients

The age and sex of all patients included in this series are shown in table 1: 82 were male and 18 female. Age ranged from 31 years to 77 years and averaged 57 years. The group exhibited the distribution in sex and age characteristic of coronary disease in general. The 15 "control" patients were similar in average age and in sex distribution.

Presenting symptoms at the time of diagnosis in the 100 cases are shown in table 2. Patients in the "control" group were comparable to the treated group. The largest group consists of 45 patients who described the occurrence or onset of characteristic cardiac ischemic pain, which they had never had before. In this group a few patients began as angina of effort, which progressed rapidly, but in all cases one or more episodes of pain at rest had occurred before the diagnosis was made. Duration of symptoms prior to inclusion in the series varied from 1 day to 5 months, with an average of 16 days. Significantly, in 15 patients the duration of symptoms was 1 day or less.

The second most common mode of presentation was that of a rapidly progressive intensification of preexisting angina of effort. This occurred in 30 patients. In these patients angina had been present from 2 months to 15

Table 2

Presenting Symptoms in Impending Myocardial Infarction

Manifestation	Onset of new progressive cardiac pain	Intensification of chronic angina	Recurrence of pain after previous infarction	Total
Duration				
Average (days)	16	13	7	
Range	1 day to 5 months	1 day to 5 months	1 day to 1 month	
Total cases	45	30	25	100
Anticoagulant	38 (45%)	24 (28%)	23 (27%)	85
"Control"	7 (47%)	6 (40%)	2 (13%)	15

years, with an average duration of 23 months. The period of intensification of symptoms varied from 1 day to 5 months and averaged 13 days.

The third group consisted of 25 patients with previous myocardial infarction in whom cardiac pain recurred after a pain-free interval of weeks, months, or years. The interval elapsing between the old infarction and the recurrence of fresh ischemic pain ranged from 1 month to 10 years and averaged 28 months. The duration of the new premonitory symptoms of an additional impending infarction ranged from 1 day to 1 month and averaged 7 days. It is apparent that these patients, having previously experienced an episode of infarction, reported the recurrence of pain much sooner than did the other 2 groups.

Duration of symptoms in the treated and "control" groups is compared in table 3. In the treated group, the duration of symptoms before diagnosis and administration of anticoagulants averaged 13 days. In the "control" group, duration of symptoms prior to diagnosis averaged 10 days. The interval from onset of symptoms to initiation of treatment in the treated cases, and the interval from onset of symptoms to the occurrence of infarction in the "controls," may be considered to be the numbers of days of "impending." It is seen that this interval was 13 days for the treated patients and 15 days for the "controls." In the "control" patients there thus existed a period averaging 5 days during which anticoagulants could have been administered.

Of the total series of 100 patients, 34 were obese, 20 had persistent diastolic hypertension, and 5 were diabetic. Incidence of these conditions was not significantly different in the treated and "control" groups.

Electrocardiograms were taken on all patients at the time diagnosis was established. In the 25 patients with known previous infarction, the old infarct was recognizable in 24, the remaining record showed marked left ventricular hypertrophy with S-T depression. Comparison with previous electrocardiograms indicated the presence of recent ischemia in 13 of the 24 patients (52 per cent).

In 75 patients without known previous infarctions, 13 patients (17 per cent) had normal records, 58 patients (77 per cent) had evidence of ischemia, and the remaining 4 showed left ventricular hypertrophy. Eleven of the 13 normal records remained normal and 35 of the 58 ischemic records improved.

Of the 15 "control" patients, 4 had normal tracings, 8 showed ischemia, 2 revealed old infarcts with recent ischemia, and 1 indicated left ventricular hypertrophy.

Results of Treatment

It is difficult to assess the effect of treatment in impending infarction without taking into account the duration of treatment and its relationship to the time at which symptoms of "impending" are first manifest. Accordingly the first 6 weeks after diagnosis have been arbitrarily considered to be the "acute phase," the period from 7 weeks to 6 months the "chronic phase," and from 6 months onward the "late phase." Table 4 shows the outcome of the 85 treated patients compared to the 15 "control" patients in each of these phases.

In the 15 "control" patients it is almost

incredible to find that 14 infarcted. Of these, 11 were fatal and 3 were nonfatal. One of the patients with nonfatal infarction died of congestive heart failure 18 months later. One patient, a man of 66 years at the time of diagnosis, rested at home but remained ambulant for 2 months, and subsequently remained well except for mild angina of effort. The 3 nonfatal infarcts occurred from 3 to 4 days after diagnosis of impending infarction had been made. The 11 fatal infarctions occurred from 3 to 92 days (average 20 days) after diagnosis. However, if 2 patients who survived 56 days and 92 days respectively are excluded, the remaining 9 fatalities occurred on an average of 8 days after diagnosis, (range 3 to 19 days). Thus 12 patients infarcted, 9 of them fatally, during the "acute phase." Two of the 3 patients who reached the "chronic phase" then infarcted fatally.

Unfortunately no autopsies were performed in this group, as 8 patients died outside hospital and in the other 3, permission for necropsy was not granted. The manner of death was observed by a physician in 7 patients, and there seemed no doubt of infarction in 5, and that infarction was probable in 2. In 3 patients, death was sudden and unobserved. Three patients lived long enough to reach the hospital but died shortly after admission. In these patients, electrocardiograms confirmed acute myocardial infarction.

In no instance was infarction associated with undue effort or emotion. Two of the nonfatal attacks occurred while the patients were in bed and 1 while the patient was sitting in a chair. Eight of the fatal attacks occurred while patients were in bed, the other 3 during the ordinary activity of a housewife, a physician, and a merchant. It therefore does not seem reasonable to attribute these deaths to undue exertion or to lack of rest alone. One can only speculate about the probable outcome in these patients had anticoagulants been given, but in the light of results in treated patients, now to be presented, it seems likely that more would have survived.

Of the 85 patients who received anticoagulants during the "acute phase," only 2 had infarcts and neither of these was fatal. One of them occurred when the prothrombin time was temporarily above the therapeutic range. In 5 patients, anticoagulants were discontinued during this phase. Of the 80 patients carried on treatment to the "chronic phase," 3 infarcted, 2 being fatal. In the "late phase," reached by 57 treated patients, 10 suffered infarctions and 7 of these were fatal.

Table 3

Duration of Symptoms in Treated and "Control" Patients

	Anticoagulant	"Control"
Days of symptoms before diagnosis	13	10
Days "impending"	13	15

The benefits of anticoagulants in the "acute" and "chronic" phases appears substantial. Although the data are not susceptible to statistical analysis, the striking difference in outcome between the treated and "control" patients strongly suggests that anticoagulants exert a protective influence in the state of impending infarction. The incidence of fatal infarction and sudden death in the "chronic phase" appears to be a matter of the influence of long-term anticoagulants in patients with chronic coronary disease, rather than in the more restricted state of "impending infarction."

Ideally, one would prefer to have a large series with alternate patients serving as controls. In the present series the "controls" were selected in part by the patients, and in part by the chance unavailability of hospital accommodation. However, there was striking similarity to the treated groups in respect to age, sex, mode of presentation, duration of symptoms, and electrocardiographic findings.

The outcome in the 29 patients in whom anticoagulants were eventually discontinued is of interest. In 13 patients who had been treated for an average of 47 weeks (range 3 to 244 weeks), infarction occurred at a variable period after anticoagulants were discontinued. Of these, 4 were fatal and 9 were non-

Table 4

Outcome in Treated and "Control" Groups

	Entire series	"Controls" Acute phase 0—6 wks.	"Controls" Chronic phase 7 wks.—6 mos.	Anticoagulant Acute phase 0—6 wks.	Anticoagulant Chronic phase 7 wks.—6 mos.	Anticoagulant Late phase Over 6 mos.
No. of patients	100	15	3	85	80	57
No. of infarcts	42*(42%)	12	2	2†	3	10
No. of deaths	24*(24%)	9	2	0	2	7

*Includes those occurring after anticoagulants were discontinued.
†One with prothrombin time above therapeutic range.

fatal. Seven infarcts (3 fatal) occurred in the first 6 weeks after withdrawal, 6 (1 fatal) occurred over 6 weeks after withdrawal. It is impossible to know how many of these might have occurred even with continuation of treatment. A further 16 patients who had been on anticoagulants for an average of 24 weeks (range 2 to 131 weeks) had no cardiac complication on withdrawal but 2 suffered nonfatal cerebral thromboses. In the 6 patients in whom anticoagulants were discontinued because of bleeding, 3 infarcted, and 2 of these were fatal.

Outcome was not significantly influenced by the presenting symptoms. As might be expected, more infarctions occurred during anticoagulant treatment in those patients with previous chronic angina and in those with previous infarctions, but the small numbers of patients do not permit of valid deductions.

Complications of Treatment

Two unusual complications were encountered. One patient with a history of a previous infarction was given Danilone when symptoms of impending infarction developed. Due to excessive hypoprothrombinemia, hematuria and large ecchymoses occurred. Emulsified Vitamin K_1 (Mephyton) was administered intravenously and was immediately followed by a severe hemolytic reaction. Fortunately, the patient recovered. This appears to be the first instance of a reaction to the antidote to therapeutic hypoprothrombinemia.[21]

Another patient, with chronic angina of effort, was treated with Danilone when symptoms abruptly intensified. A sensitivity reaction to Danilone,[22] characterized by hepatitis, dermatitis, and pyrexia, developed at the fifteenth day. Prompt recovery from the reaction followed administration of prednisone.

The main complication in this series was hemorrhage. During a total of 6,484 patient-weeks of therapy, hemorrhage occurred on 37 occasions. In 15 patients the bleeding consisted of hematuria, and in 6 patients epistaxis occurred. In 27 patients the hemorrhage was of minor degree and did not necessitate more than simple local measures and the temporary withholding of further anticoagulants. In 10 patients the bleeding was considered of major proportions and necessitated hospital treatment; in 6 cases the source of this severe bleeding was from the gastrointestinal tract. In no case was death directly attributable to hemorrhage although in 2 instances hemorrhage necessitated the discontinuance of anticoagulants and this in turn was promptly followed by fatal infarction.

Discussion

Despite its potential importance, little attention has been paid to recognition of impending infarction. Perhaps this lack of interest has been due, until recently, to inability to alter the outcome significantly. Prior to the advent of anticoagulants the principal treatment advocated has been rest,[23] but it has been stated[24] that only a small number of infarctions are provoked by undue demands on the heart, and many occur at rest, even during sleep. Now with the demonstrated value of anticoagulants, particularly during the "acute phase" of impending infarction, early recognition is of great consequence.

Reference has been made to the incidence of

premonitory symptoms preceding myocardial infarction.[6, 11, 12] In a recent study, Maurice et al.[25] pointed out that in an impressive minority of cases, (39 per cent) infarction is not an unforeseeable event but is heralded by symptoms varying from a few hours to a month or more. Clinical features of their patients were similar to the present series, but more of them presented as an intensification of preexisting angina of effort.

Although it has taken nearly 9 years to assemble the present series, a more or less gradual increase in frequency of this diagnosis has been observed over the years. Part of this increase is no doubt due to the increasing number of cardiac patients seen by the authors but a portion of the increase is also due to a program of education of patients, whereby all patients with coronary disease are instructed to report to the physician any appreciable change in their cardiac pain. As a result more patients come under medical observation before they have progressed to the stage of actual infarction. If the preventive measures of anticoagulation and rest are of value, this program of patient education is important. There is, of course, the disadvantage that the physician is frequently informed of insignificant pains but after a few discussions patients soon learn which pains to report and which to ignore. In any case the advantages of early reporting of pain are considered to outweigh by far the occasional annoyances. This procedure might be crudely compared to having patients report potentially premalignant lesions to the physician before established cancer has occurred.

As early as 1944, Bayley and LaDue[26] described the electrocardiographic findings of impending infarction and stated, "if infarction can be prevented or minimized at its impending stage, the recognition of this stage would be important clinically." Although the electrocardiogram provides welcome confirmatory value when abnormal, it is emphasized that 17 per cent of the present series, and 29 per cent of the patients of Maurice et al.[22] had normal records.

The pathologic basis of impending infarction is even less well understood than the mechanism of coronary occlusion itself. Parkinson and Bedford[27] considered that the prodromal pain announced the beginning of coronary thrombosis while the subsequent myocardial infarction marked complete occlusion. When premonitory symptoms develop abruptly, it seems likely that an acute change has occurred in the coronary circulation, whether it be thrombosis, subintimal hemorrhage, or occlusion by a plaque. The incidence and role of subintimal hemorrhage in production of coronary occlusion is not agreed upon, but its possible presence is sometimes stated to be a contraindication to the use of anticoagulants. In view of the beneficial effects of anticoagulants noted in this and other series, it would appear that either subintimal hemorrhage is not aggravated by anticoagulants, that secondary thrombosis in relation to the subintimal hemorrhage is prevented, or that it is not a common event.

Because the period of prodromal symptoms is often short, there is urgency in achieving anticoagulant effect. Thus the more quickly acting oral anticoagulants have an advantage. The necessity for heparin at the initial stage has not been established but its use seems rational. Maurice et al.[25] used it in 46 of 71 patients. In the present series it was used in 21 of the 85 patients; in none of these did death or infarction occur during the "acute phase," but 1 patient, adequately controlled, died 20 weeks later.

The reported incidence of infarction (usually 30 to 50 per cent) and of fatality (15 to 43 per cent) in patients with prodromal symptoms has been mentioned. The reduction of both by use of anticoagulants in this series is impressive, both by comparison with a "control" series and with published studies. Further support is afforded by results of anticoagulant therapy of impending infarction reported by several authors. Wood[1] treated 33 patients with "acute coronary insufficiency" with a result of 2 infarcts and no deaths; in 25 similar untreated cases there

were 12 infarcts and 5 deaths. Nichol et al.[28] recently reported 6 per cent mortality in 96 treated patients and 18 per cent mortality in 32 patients abandoning treatment. Maurice et al.[25] observed only 2 infarctions in 71 patients and were impressed with the fact that 64 per cent of patients became free of pain. The similarity in these reports is persuasive.

The mechanism causing death in patients with coronary atherosclerosis is often not clear, even after autopsy examination. Patients may die with no evidence of infarction, and patients with infarcts may live with little manifestation of the cardiac lesion. In assessing the effect of anticoagulants in patients with coronary disease, it is necessary to take into account not only the infarctions which may or may not be prevented, but also the reduction in "sudden deaths" by whatever mechanism.

Summary

Coronary occlusion with myocardial infarction is a common condition with a high mortality. The mechanism of coronary occlusion in such cases is not always clear, but thrombosis, either directly or indirectly, is a dominant process.

In many instances premonitory symptoms give warning that myocardial infarction is threatening. It is suggested that these symptoms form a recognizable pattern which permits recognition of impending myocardial infarction with a high degree of accuracy. Three common presentations are described.

Frequency of diagnosis of impending infarction may be increased by a program of patient education.

Prompt administration of anticoagulants appears to influence the outcome favorably, particularly in the first few days or weeks of symptoms.

Summario in Interlingua

Occlusion coronari con infarcimento myocardial es un condition common con alte cifras de mortalitate. Le mechanismo del occlusion coronari in tal casos non es semper clar, sed thrombose—directe o indirecte—es un processo dominante.

In multe casos symptomas premonitori annuncia le imminente infarcimento myocardial. Es opinate que iste symptomas forma un recognoscibile ensemble que permitte le recognition del veniente infarcimento myocardial con alte grados de accuratia. Tres situationes commun es describite.

Le frequentia del diagnose de imminentia de infarcimento myocardial pote esser augmentate per un programma de education del patiente.

Il pare que le prompte administration de anticoagulantes exerce un influentia favorabile super le resultato final, specialmente durante le prime dies septimanas del symptomas.

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Vesalius

"My study of anatomy," says Vesalius, "would never have succeeded had I when working at medicine at Paris been willing that the viscera should be merely shewn to me and to my fellow students at one or another public dissection by wholly unskilled barbers, and that in the most superficial way. I had to put my own hand to the business." . . .

Complete dissection was then well-nigh impossible, the most that could be gained was the hurried examination of some parts of the body of a patient who had succumbed to disease. One part of the human body, the foundation of all other parts, the skeleton, could however be freely used for study. In those rude times burial was rough and incomplete, and in the cemeteries bones lay scattered about uncovered. In the burial-ground attached to the church of the Innocents at Paris Vesalius spent many hours, studying the bones; and he also tells us how in another burial-ground, on what is now 'Les Buttes Chaumont,' he and a fellow student nearly left their own bones, being on one occasion attacked and in great risk of being devoured by savage, hungry dogs who too had come there in search of bones. By such a rough, perilous study Vesalius laid the foundation of his great work, a full and exact knowledge of the human skeleton.—SIR M. FOSTER. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

Stenosis of the Right Main Pulmonary Artery

Clinical, Angiocardiographic, and Catheterization Findings in Ten Patients

By LAWRENCE L. LUAN, M.D., JOSEPH LLOYD D'SILVA, M.D., BENJAMIN M. GASUL, M.D., AND ROBERT F. DILLON, M.D.†

ISOLATED stenosis of a branch of the pulmonary artery is not a rare anomaly in our experience; however, there have been few published reports of this condition. Multiple stenosis in one or both pulmonary arteries has been more frequently reported.

Sondergaard[1] reported 3 patients with stenosis of the main pulmonary artery at the point where it was joined by the ligamentum arteriosum. He called this anomaly "coaretation of the pulmonary artery." Schumacher and Lurie[2] cited a similar case in a 14-year-old girl. Recently Hodges,[3] Powell,[4] and Coles and associates[5] reported cases of narrowing of both right and left pulmonary arteries at the bifurcation of the main vessel diagnosed by angiocardiographic and cardiac catheterization studies.

Gyllenswörd and co-workers[6] and Arvidsson's group[7] reported 12 cases of multiple stenosis in both branches of the pulmonary artery that were demonstrated by dextro-angiocardiographic studies. Eldridge and collaborators[8] described 5 patients with stenosis of a branch of the pulmonary artery, 3 of which occurred on the right, 1 on the left, and 1 was bilateral.

The purpose of this paper is to report 10 patients with stenosis of the right pulmonary artery, in all of whom the diagnosis was confirmed by cardiac catheterization and dextro-angiocardiographic studies. They ranged in age from 4 months to 13 years. Four were males and 6 females. Of these, 7 cases had associated cardiac anomalies as follows: 1 with pulmonary valvular stenosis, 1 with pulmonary valvular stenosis and patent ductus arteriosus, 2 with patent ductus arteriosus only, 2 with ventricular septal defects, and 1 with tetralogy of Fallot.

The physical findings depended on the other cardiac anomalies. The effect of the stenotic pulmonary artery alone was assessed by clinical, angiocardiographic, electrocardiographic, roentgenologic, and hemodynamic data obtained in all of the 10 patients; in 2 patients with patent ductus arteriosus these data were also obtained postoperatively.

Case Reports

Case 1

An 8-year-old girl was admitted to the cardiac clinic because of a heart murmur. The blood pressures in the right arm and left leg were 120/80 and 134/80 respectively. The heart was not enlarged to percussion. S_1 was normally split and maximum at the apex; S_2 was normally split and maximum at the second left intercostal space; S_3 was constant at the apex. There was a soft grade-III systolic murmmur heard best in the second and third intercostal spaces near the sternum as well as over the second right intercostal space and transmitted to the back. Roentgenograms of the chest revealed no cardiac enlargement. An electrocardiogram showed left axis deviation and an incomplete right bundle-branch block. Angiocardiograms* revealed slight dilatation of the main pulmonary artery. Right heart catheterization demonstrated stenosis of the right main pulmonary artery and no shunt between the pulmonary and systemic circulations (tables 1 and 2).

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Aided in part by a grant from the Chicago Heart Association and Grant H-3518, U. S. Public Health Service.

†Deceased.

*The angiocardiograms on all the cases reported were taken with the Elema apparatus at 8 or 4 per second simultaneously in the posteroanterior and lateral views.

Table 1

Intravascular Pressures Obtained from Catheterization on Ten Patients with Isolated Right Pulmonary Artery Stenosis and Associated Defects

Cases		Systemic artery S	D	M	Right ventricle S	D	M	M.P.A. S	D	M	R.P.A. distal to stenosis S	D	M	Gradient across the stenosis S	D	M
1		123	89	103	23	2	11	23	8	16			10			6
2		115	72	85	37	2	23	34	10	20	11	7	8	23	3	12
3		83	59	71	40	1	20	38	8	21			11			10
4					64	4	23	20	10	11						
5	Preop.	87	50	68	67	6	24	90	47	61	32	15	21	58	32	40
	Postop.	134	81	103	59	3	27	37	12	23	24	11	19	13	1	4
6		116	75	90	42	4	21	44	19	34	24	15	25	20	4	9
7	Preop.	169	66	95	76	4	39	76	58	64			30			34
	Postop.	115	80	97	47	3	26	54	15	29	16	9	10	38	6	19
8		110	60		53	2	25	53	12	27	30	12	18	23	0	9
9	1st	80	50	62	62	2	34	62	22	43						
	2nd	113	78	89	43	3	21	42	14	26	26	14	19	16	0	7
10	1st*	105	65	84	54	4	29	52	23	40	52	23	40	0	0	0
	2nd	165	58	79	95	0	44	38	12	24	26	11	16	12	1	8

*In retrospect, reviewing the spot films taken during the 2 catheterizations, it was found that the pressure of 52/23 mm. of mercury recorded in the first catheterization was proximal to the stenosis as correlated with the angiograms. The pressures taken during the second catheterization show a definite systolic pressure gradient between the right pulmonary artery and the main pulmonary artery. The spot films taken at the time of the second catheterization indicate that the tip of the catheter was beyond the stenotic area visualized on the angiogram.

R.P.A., right pulmonary artery; M.P.A., main pulmonary artery; S, systolic pressure; D, diastolic pressure; M, mean pressure.

Case 2

An asymptomatic 8-year-old girl was admitted for cardiac evaluation. Blood pressures were 110/70 and 114/70 in the right arm and leg respectively. The heart was not enlarged to percussion. S_1 and S_2 were normal in intensity. A grade-III harsh systolic murmur was heard over the second left and right intercostal spaces. It was transmitted well to the back in the interscapular region. Roentgen rays of the chest and the electrocardiogram were within normal limits. A diagnosis of stenosis of the right pulmonary artery was made. Right heart catheterization and selective angiocardiogram confirmed the clinical diagnosis of isolated stenosis of the right main pulmonary artery (tables 1 and 2). A selective angiocardiogram showed definite stenosis of the right pulmonary artery with poststenotic dilatation.

Case 3

A 16-month-old Negro girl with no cardiac symptoms was admitted for diagnosis of a heart murmur discovered at the age of 2 months. Blood pressure in the left arm was 84/60. The apex of the heart was in the fourth left intercostal space at the midclavicular line. A systolic thrill was felt over the third and fourth left intercostal spaces, maximum over the fourth. S_1 was normal in intensity and maximal at the apex; S_2 was split and normal in intensity. A harsh grade-IV systolic murmur was heard all over the precordium maximal at the third and fourth left intercostal spaces and was well transmitted to the back. Electrocardiogram showed right bundle-branch block with right ventricular hypertrophy. Cardiac catheterization and angiocardiography demonstrated stenosis of the right main pulmonary artery (tables 1 and 2).

Case 4

A 4-month-old girl was referred to the cardiac clinic because of cyanosis and dyspnea at 3 weeks of age. Blood pressures (flush method) of the left arm and left leg were 58 and 68 mm., respectively. The apex of the heart was in the fifth left intercostal space just outside the midclavicular line. S_1 was loudest in the second left intercostal space; S_2 was split and maximal over the second right intercostal space. A grade-II to -III systolic murmur was heard over the aortic and pulmonary areas, radiating down the left sternal border and transmitted to the interscapular region on the right. An electrocardiogram showed right ventricular hypertrophy. Angiocardiograms revealed stenosis of the pulmonary valve and the right main pulmonary artery with decreased vascularity of the right lung field. Findings on right heart catheterization were consistent with a diagnosis

Table 2

Gasometric Determination of Blood Samples Obtained at Catheterization

Cases		Pulmonary artery		Right ventricle		Right atrium		Cavae		Systemic artery	Saturation (%)
		Rt.	Main	Inflow	Outflow	Upper	Lower	sup.	inf.		
1		11.17	11.16	11.17		10.76	10.92	10.05	12.11	14.17	96.1
2		11.25	10.69			10.06	10.86	10.43		15.50	96.6
3		10.35	10.15	9.93	9.77	9.79	9.19	12.23	9.25		
4			10.4	10.42	10.56	10.89	10.04	8.40	11.07		
5	Preop.	11.78	14.58	10.99	10.96	10.77	11.22	10.75	11.93	15.38	98.3
	Postop.	11.92	12.01	12.00	12.15	11.65	12.35	11.57	10.61	16.71	98.1
6		14.72	15.13	11.57	11.67	11.73	11.89	11.77	12.45	15.46	94.8
7	Preop.	13.70	15.04	10.40	11.72	10.44	10.32	10.68		15.09	95.7
	Postop.		12.75	11.98	12.40	12.17		11.62		16.51	97.6
8		10.22	10.22	9.40	9.57		7.87	8.04	8.09		
9	1st		11.39	9.99	11.53	6.72	7.05	6.86	6.62	12.32	98.3
	2nd	14.20	13.97	12.61	14.76	10.55	10.64	12.02	11.25	14.60	
10	1st	10.81	10.59	10.44	10.13	9.31	9.38	9.29	9.96		97.2
	2nd		13.39	12.51	13.10	12.03	11.89	11.71	13.80	16.20	97.8

of isolated pulmonary valvular stenosis. A gradient could not be demonstrated between the main pulmonary artery and the stenotic right pulmonary artery, since the catheter could not be advanced into the right pulmonary artery (tables 1 and 2). A diagnosis of pulmonary valvular stenosis and isolated stenosis of the right main pulmonary artery was made on the basis of the catheterization and angiocardiographic findings.

Case 5

A 4-year-old Negro boy was admitted to the cardiac clinic with a history of frequent episodes of upper respiratory infection. The blood pressures in the right and left arms were 112/50 and 108/50, respectively. The heart was not enlarged. A systolic thrill was felt with maximum intensity in the second and third left intercostal spaces and suprasternal notch. S_1 was split, of low frequency, normal intensity, and duration; S_2 was well heard at the second left intercostal space where it was split with a dominant aortic component. A grade-IV systolic murmur was best heard in the second left intercostal space and was widely conducted to the left, both in front and back. A grade-IV systolic and diastolic murmur of continuous type was heard best over the second left intercostal space close to the sternum. Roentgenograms showed a mild prominence of the pulmonary artery and enlargement of the left ventricle and atrium. Electrocardiograms showed right and left ventricular hypertrophy. Angiocardiograms revealed poor opacification of the right lung field and blanching at the level of the main pulmonary artery. Right heart catheterization confirmed the diagnosis of stenosis of the right pulmonary artery and patent ductus arteriosus.

After ligation of the ductus examination revealed a systolic murmur over the second and third left intercostal spaces that was transmitted to the back. Repeat right heart catheterization revealed a stenosis of the right pulmonary artery and valvular stenosis (tables 1 and 2).

Case 6

A 4½-year-old Negro girl was admitted to the clinic because of occasional dyspnea and easy fatigability. Examination revealed increased suprasternal and carotid pulsations and pistol-shot femoral pulses; the blood pressure was 116/75. The apical impulse was in the fifth left intercostal space at the anterior axillary line. A systolic and diastolic thrill and murmur typical of a patent ductus were noted over the upper left intercostal spaces. The murmur was transmitted to both sides of the chest. Roentgenograms showed moderately increased pulmonary blood flow with left ventricular enlargement. An electrocardiogram revealed diastolic over-filling type of left ventricular hypertrophy. Right heart catheterization showed mild pulmonary hypertension with a marked drop in pressure as the catheter was advanced from the main pulmonary artery into the right pulmonary artery, indicating stenosis of the right pulmonary artery and evidence of a patent ductus arteriosus. Angiocardiograms were confirmatory (tables 1 and 2).

Case 7

A 13-year-old Negro boy was referred to the cardiac clinic for a heart murmur. Neck veins were distended and there was a definite increase in arterial pulsation in the neck. The blood pressure was 168/68 and the femoral pulses were bounding. The fingers of both hands were tapered.

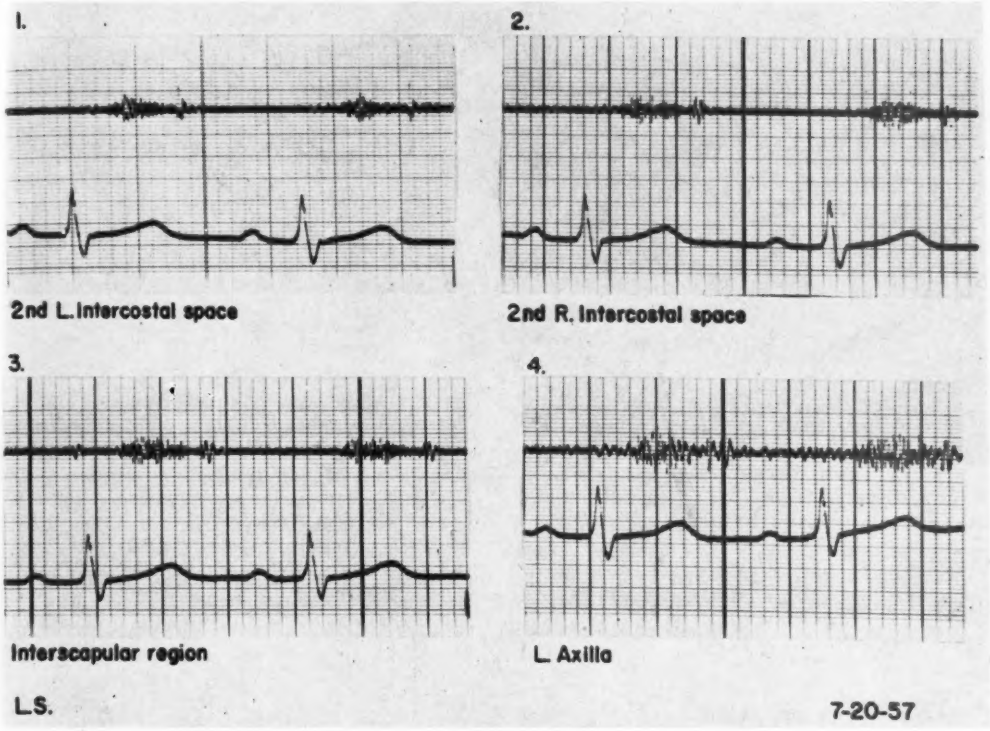

Figure 1

Phonocardiogram, in a case of isolated stenosis of the right pulmonary artery at its bifurcation from the main pulmonary artery, shows the systolic murmur in the second left and right intercostal spaces and transmitted to the interscapular region and left axilla.

The apex of the heart was at the fifth left intercostal space just outside the midclavicular line. Besides the typical findings of patent ductus arteriosus, there was a systolic murmur over the aortic area radiating to the neck with a soft diastolic component. Roentgenograms and fluoroscopy revealed increased hilar pulsations and vascular markings in the left lung field. Electrocardiograms showed left ventricular hypertrophy. Angiocardiograms revealed the left pulmonary vasculature well outlined compared to the right and evidences of a patent ductus arteriosus. Right heart catheterization (tables 1 and 2) revealed stenosis of the right pulmonary artery and patent ductus arteriosus with marked pulmonary hypertension. There was a marked decrease in pressure as the catheter was advanced into the right pulmonary artery close to its origin from the main branch; the pressure tracing had only a vibratory pattern without the distinguishable systolic and diastolic form. Analysis of the blood samples revealed a left-to-right shunt at the aortic-pulmonary level. A preoperative diagnosis of patent ductus arteriosus, stenosis of the right main pulmonary artery, and Marfan's syndrome was made. The ductus was ligated, and the postoperative recovery was uneventful. Examination after ligation of the ductus revealed a grade-IV systolic murmur heard over the aortic area, transmitted to the back and to the right side. Repeat right heart catheterization demonstrated stenosis of the right pulmonary artery and a decrease in the pulmonary hypertension.

Case 8

A 4-month-old Negro girl was admitted to the hospital for cardiac evaluation. The blood pressures in the right arm and right leg were 100/60 and 110/60, respectively. Cardiac examination revealed a forceful apical beat at the fifth intercostal space in the anterior axillary line. A thrill was felt at both the base and the apex. S_1 was increased in intensity, split, and best heard at the apex. S_2 was split, normal in intensity, and best heard in the second left intercostal space. A

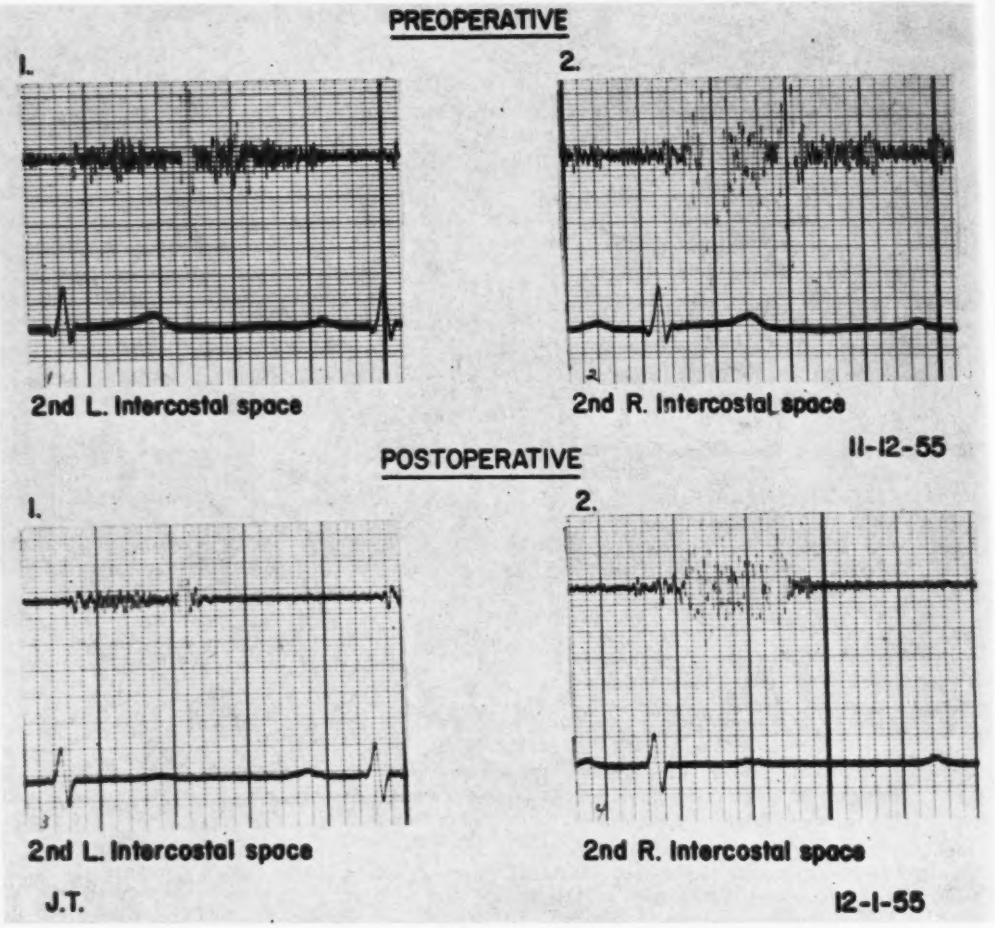

Figure 2

Preoperative phonocardiogram, in a case of isolated stenosis of the right pulmonary artery distal to the bifurcation of the main pulmonary artery with patent ductus arteriosus, does not show the typical murmur of patent ductus. Postoperatively only the systolic murmur persisted, still heard best in the second right intercostal space.

grade-V harsh pansystolic murmur of a ventricular septal defect was heard along the left sternal border with maximum intensity over the fourth left interspace; it was transmitted to the apex, axilla, and back. Roentgenograms showed increased pulmonary vascular markings and left atrial and ventricular enlargement. An electrocardiogram revealed right ventricular hypertrophy. Angiocardiograms showed stenosis of the right pulmonary artery and evidence of a ventricular septal defect. Right heart catheterization confirmed the diagnosis (tables 1 and 2).

Case 9

A 27-month-old Negro boy was admitted for cardiac evaluation. A clinical diagnosis of a ventricular septal defect was made at the age of 6 weeks and was confirmed by cardiac catheterization. The branches of the pulmonary artery were not entered so that their condition was not known (tables 1 and 2). The blood pressures were 90/60 and 100/60 mm. over the right arm and leg respectively. A diffuse apical impulse was felt in the fifth left intercostal space at the anterior axillary line. There was a thrill at the lower left

sternal border. A typical murmur of ventricular septal defect was heard, but it was transmitted to the axilla and the back. A grade-II diastolic rumble was heard at the apex. Roentgenograms of the chest showed evidence of increased pulmonary blood flow and left atrial and ventricular enlargement. Electrocardiograms showed left ventricular hypertrophy. Right heart catheterization demonstrated a ventricular septal defect with slightly decreased pulmonary artery pressure, as well as stenosis of the right pulmonary artery (tables 1 and 2). Angiocardiograms revealed the existence of both the ventricular septal defect and a dilated main pulmonary artery which was larger than the aorta, with stenosis of the right pulmonary branch.

Case 10

A 3-year-old Negro boy with a clinical diagnosis of ventricular septal defect, confirmed by angiocardiograms and right heart catheterization (tables 1 and 2), was admitted for re-evaluation of cyanosis of recent onset. The blood pressures were 90/50 and 100/50 in the right arm and left leg, respectively. A grade-III pansystolic murmur and thrill were noted at the second left intercostal space. S_2 was loud and split and best heard over the second left intercostal space, close to the sternal border. Right heart catheterization revealed a bidirectional shunt at the ventricular level, pulmonary stenosis of the infundibular type, right ventricular hypertension, and stenosis of the right pulmonary artery (tables 1 and 2). Angiocardiograms showed early opacification of the aorta and diminished vascularity of the right lung. A diagnosis of tetralogy of Fallot was made and the patient was operated on with use of a pump oxygenator. He had an uneventful postoperative recovery.

Discussion

No satisfactory etiology has been given to explain the occurrence of stenosis in the right pulmonary artery. A congenital developmental defect has been cited. That absence of a pulmonary artery or its stenosis has been reported more often on the right side, suggests a common embryologic explanation for both these anomalies. The pulmonary arch is formed by the establishment of a connection between the dorsal aorta and a pair of arteries extending backward from the aortic sac. This is joined by the primitive pulmonary artery. Next, on the right side, the segment of the arch lying distal to the primitive pulmonary artery degenerates. The angle between its proximal part and the primary artery is gradually lost and the segment now forms part of the proximal segment of the adult right pulmonary artery. The distal segment of the left pulmonary arch, however, does not degenerate but forms the ductus arteriosus of the full-term fetus. Embryologically, the main pulmonary trunk is anatomically to the left of the aorta in the midsagittal plane and therefore its left branch has a much shorter and more direct route to the dorsal aorta and thus receives a better and more direct blood supply. Madoff and co-workers[9] suggested that these factors might explain the occasional absence of the right pulmonary artery occurring more often on the right than on the left. Isolated stenosis of the right pulmonary artery may be an intermediate stage between the normal development or complete absence of the right pulmonary artery.

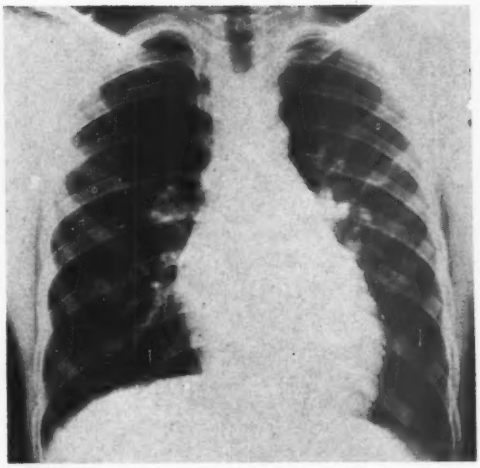

Figure 3

X-ray of the chest of a patient with isolated stenosis of the right pulmonary artery shows decreased vascularity of the right lung field.

We are concerned here with isolated stenosis of the right main branch of a pulmonary artery, with or without associated anomalies. The cases of multiple stenosis of the smaller branches of the pulmonary arteries may very well be due to developmental anomalies that occur in the transformation of the primitive pulmonary artery from the plexus of vessels

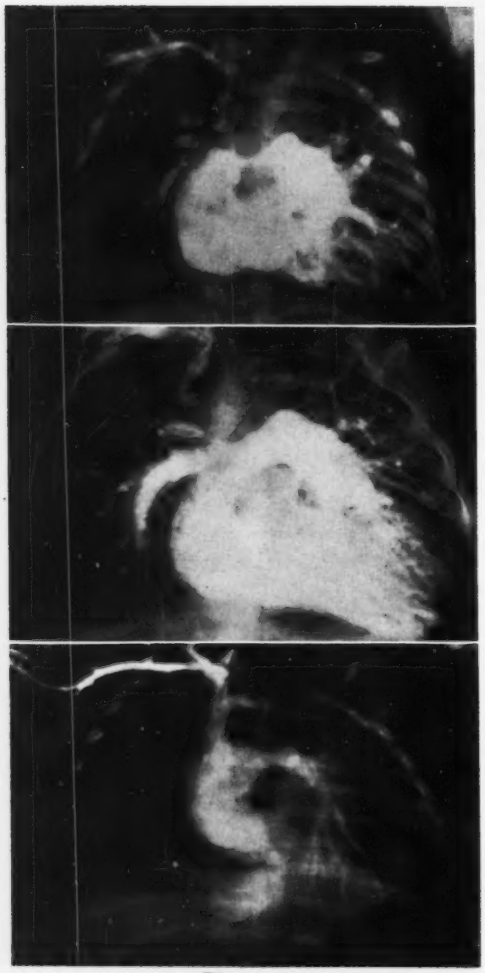

Figure 4

Dextroangiocardiograms demonstrating the site of the stenosis of the right main pulmonary artery with disproportionate opacification of the lung fields.

to its adult form. Pulmonary embolism with partial recanalization could result in single or multiple sites of narrowing in branches of both pulmonary arteries. However, pulmonary embolism is unlikely in our group of young patients. Williams, Lange, and Hecht[10] have shown that a considerable degree of constriction must exist before a measurable pressure gradient in the pulmonary artery can be obtained for a given flow. They also demonstrated that a 50 per cent reduction in diameter will result in a drop of only 9 mm. of mercury mean pressure across the constriction. It is obvious, therefore, that minimal stenosis may occur without demonstrable pressure change. Conversely, when the flow and pressure are raised, as in the presence of a patent ductus arteriosus (cases 5 and 7) or in the presence of a ventricular septal defect, a high gradient may occur even though the stenosis may be mild. A moderate stenosis with a coexistent pulmonary valvular (case 4) or infundibular stenosis may only be detected after the latter abnormalities are relieved. It is quite possible that the diastolic murmur heard in our case 7, who also had an associated patent ductus arteriosus, was not due to the ductus alone, in that there was a wide diastolic gradient across the stenotic area prior to surgery. The reduction in this diastolic pressure gradient following ligation of the patent ductus is easily explained by the resultant reduction in pulmonary blood flow, with consequent disappearance of the diastolic murmur due to both the ductus and the stenotic pulmonary artery.

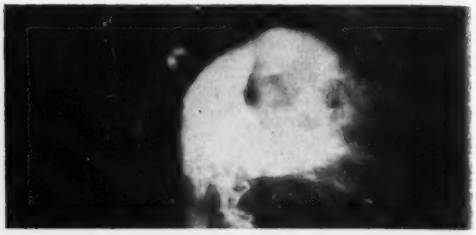

Figure 5

Dextroangiocardiogram shows overlapping of the right atrial appendage obscuring the stenotic right main pulmonary artery.

In recent years, this anomaly has been diagnosed with increasing frequency by both clinical and laboratory means. We presume that the normal life span of these patients should not be affected in any way by the presence of this isolated anomaly. In the past, before angiocardiography and cardiac catheterization became part of the routine investigative procedure in undiagnosed cardiac lesions, some of the so-called "functional murmurs" could

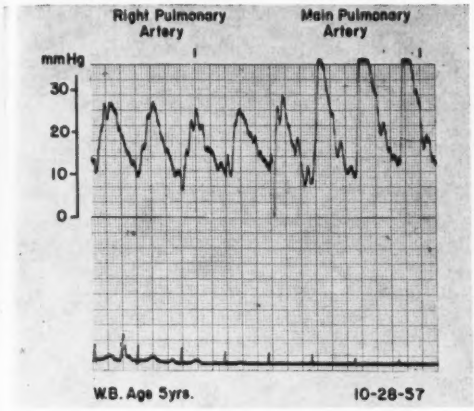

Figure 6

The pressure pulse distal to the stenotic area does not reveal the typical vibratory pattern. The diagnosis is based on the pressure gradient.

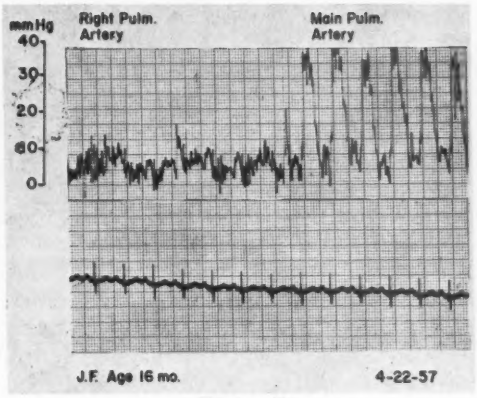

Figure 7

Pressure pulse of the right pulmonary artery distal to the stenosis shows an ill-defined vibratory curve with a sharp rise in pressure on withdrawal of the catheter into the main pulmonary artery.

very well have been due to this condition. The systolic murmur in this entity is of the midsystolic ejection type. It does not involve the first heart sound because it always starts after the closure of the atrioventricular valves. An early systolic click is not present as the normal anatomy of the pulmonary valve is not involved, and there is no dilatation of the main pulmonary artery. Since significant right ventricular hypertrophy is not present, ventricular systole is not prolonged. The second sound is normally split with normal intensity of its 2 components over the pulmonary area.

The location of the murmur depends upon whether the stenosis is at the point of bifurcation of the main pulmonary artery or distal to it. In the former site, it is maximal in the second left intercostal space and may even be transmitted to the left axilla or interscapular region (fig. 1). In the latter case (fig. 2) it is maximal in the second right intercostal space and may then be transmitted to the back.

The electrocardiogram of patients with stenosis has a normal pattern unless associated lesions are present. The roentgenograms of the chest may show evidence of decreased vascularity of the right lung as compared to the left (fig. 3). This finding, together with the systolic murmur and the normal electrocardiogram, should permit clinical diagnosis of this anomaly. Angiocardiograms usually demonstrate the stenosis of the right main pulmonary artery (fig. 4). At times, the stenotic area may not be visualized because of overlapping of the right atrial appendage (fig. 5).

Right heart catheterization in the isolated form shows no alteration in hemodynamics except for a pressure gradient across the stenotic area (fig. 6). This was obtained in all cases except 1 (case 4) in which the catheter could not be advanced beyond the main pulmonary artery. The pressure-pulse distal to the stenosis may have a vibratory curve (fig. 7), depending upon the degree of stenosis; at times this may make its identification as an artery difficult. Right ventricular and pulmonary hypertension are unlikely to occur unless other congenital cardiac defects are present.

Since the murmurs produced by this anomaly may, in many ways, resemble the group of surgically correctible acyanotic congenital heart disease, it is important to consider the existence of such an anomaly in the differential diagnosis. Foremost among these is pulmonary valvular stenosis because the character, location, and distribution of the systolic murmur usually simulate the entity under discussion. In mild or moderately severe pul-

monary valvular stenosis, however, with right ventricular pressure below 100 mm. of mercury, an early systolic click is usually present and the second sound over the pulmonary area is widely split (0.06 to 0.12 second) due to the delay in the closure of the pulmonary valves.[11] In the severe type with right ventricular pressure over 100 mm. of mercury, the markedly diminished second heart sound over the second left intercostal space, the markedly delayed closure of the pulmonary valve, the presence of a lower parasternal lift, and an electrocardiogram showing right venticular hypertrophy of the systolic overfilling type manifested as a qR or tall R over V_{4R}, V_{3R}, and V_1 with or without a tall R in aV_R, serve to differentiate it from isolated stenosis of the right pulmonary artery. In atrial septal defects, the systolic murmur that is heard best over the pulmonary area is almost always softer and of less intensity. The wide separation of the 2 components of the second sound together with its relative fixation during the respiratory cycle[12, 13] should help in the diagnosis.

On the basis of our experience with these 10 patients, we believe the auscultatory findings most common to this type of congenital anomaly is a systolic murmur of grade II to IV intensity, heard over the second and third left or right intercostal spaces, depending on the location of the stenosis. This murmur usually radiates to the axillae and the interscapular region. Both the first and second heart sounds in these cases are essentially normal; this makes the differentiation from the other acyanotic congenital cardiac lesions clinically possible, particularly if the roentgenograms demonstrated diminished pulmonary vasculature of 1 lung. A systolic-diastolic murmur reported by others as a finding in this anomaly has not been present in our group of cases, even when there was a gradient of 6 mm. of mercury in diastole across the stenotic area. Such a diastolic murmur may be present in this anomaly if there is a significant diastolic gradient across the stenotic area. In order to produce such a gradient, central pulmonary artery hypertension must be present. Gyllenswörd et al.[6] attributed the diastolic murmur to proximal pulmonary artery dilatation during ventricular systole followed by prolonged emptying into the distal segment during part of the diastolic phase. This was corroborated by experimental studies done by Eldridge et al.[8] However, Gyllenswörd's case was one of multiple peripheral pulmonary artery stenosis with central pulmonary hypertension. This mechanism cannot apply to the isolated stenosis of one branch of the pulmonary artery unless pulmonary hypertension is present due to other causes.

Summary

Ten cases of isolated stenosis of the right main pulmonary artery are presented, 7 with associated anomalies. Although right heart catheterization and angiocardiography are usually necessary to demonstrate this malformation, a knowledge of the existence of this anomaly correlated with auscultatory and roentgenologic findings may often lead to a correct clinical diagnosis.

Addendum

Since submitting this paper for publication, the authors have made a correct clinical diagnosis of this anomaly based on auscultatory and roentgenologic findings in an additional 3 patients. This diagnosis was confirmed by subsequent angiocardiography and cardiac catheterization.

Summario in Interlingua

Es presentate 10 casos de isolate stenosis del arteria pulmonar dextero-major, incluse 7 con anormalitates associate. Ben que catheterismo dextero-cardiac e angiocardiographia es usualmente necessari pro demonstrar le presentia de iste malformation, le conscie consideration de su presentia possibile, in correlation con constatationes auscultatori e roentgenologic, resulta frequentemente in le correcte diagnose clinic.

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A 20-year-old woman who had experienced repeated attacks of rheumatic fever showed signs of mitral stenosis, atrial fibrillation, and wide Q waves in leads III and aV_F. In the previous year deeply inverted T waves of pointed configuration had been present in leads II and III. The patient died of collapse following peripheral embolization. At autopsy mitral, aortic, and tricuspid stenosis with thrombosis in the left and partly in the right atrium was found. The coronary arteries were normal, but the arterioles showed extensive obliterating arteritis. In the posterior wall of the left ventricle there was a large area where the entire myocardium with the exception of a narrow subendocardial layer had been replaced by dense fibrous tissue. Extensive degenerative and fibrotic changes were present throughout the myocardium, and it is probable that the aneurysmal zone of complete fibrosis was due to confluence of islands of rheumatic myocarditis.

LEPESCHKIN

Intracardiac Injection of Radioactive Krypton

Clinical Applications of New Methods for Characterization of Circulatory Shunts

By ROBERT T. L. LONG, M.D., EUGENE BRAUNWALD, M.D., AND ANDREW G. MORROW, M.D.

IN RECENT years the efforts of many groups have been directed to the development of more refined methods for the precise characterization of cardiac shunts. The application of inhaled foreign gases and the various extensions and improvements in the dye dilution method have already proved of considerable value in the study of patients with congenital heart disease.[1] In the course of clinical studies in which the radioactive gas krypton (Kr^{85}) was inhaled[2] it was found that the isotope was slightly soluble in saline solution. When such solutions were injected into a systemic vein, the right side of the heart, or pulmonary artery, the isotope could be immediately detected in expired air and little passed through the lung into arterial blood.[2, 3] When injections were made proximal to an experimental right-to-left shunt, a significant fraction bypassed the lung and high levels were found in systemic arterial blood.[4] In other experiments injections of the dissolved gas were made into the chambers of the left heart and aorta. Under such circumstances, the appearance of the isotope in the pulmonary circulation and expired air was delayed by its passage through the systemic bed. When an injection was made into the left heart proximal to the origin of a left-to-right shunt, however, the Kr^{85} was detected almost immediately and in high concentration in expired air.[5]

Following these experimental studies, these methods were applied in the study of patients undergoing diagnostic evaluation at the National Heart Institute.[6, 7] The present report presents the experiences with these technics in 48 patients.

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Methods

Gaseous Kr^{85} was prepared for injection by equilibrating it in a sealed plastic container with sterile normal saline solution. A solution containing approximately 10 μc. per ml. was obtained when 1.5 mc. of the gas (about 2.5 ml.) were mixed with 100 ml. of saline. Solutions were prepared weekly, and were assayed by counting a diluted aliquot in the same gas flow Geiger-Müller tube* utilized for the counting of whole blood.[2] In general, 5 ml. of the solution were employed for each injection in patients above the age of 12 years and 3 ml. were given in children. The studies were carried out in a well-ventilated laboratory. During the first 3 minutes after each injection, the patient's expired air was collected in a Douglas bag, the contents of which were discarded into a fume hood, or he was allowed to exhale into a specially constructed exhaust vent over the catherization table.

For the detection of a right-to-left shunt, arterial blood samples were drawn at a constant rate into oiled heparinized syringes during the 15 seconds following the beginning of the injection. These samples were counted for 1 minute in the gas flow tube, and the radioactivity was compared to that of a blank sample obtained immediately before the injection. The result of each study was expressed as a fraction relating the corrected arterial count to the total number of counts per minute contained in the solution that was injected (the arterial Kr^{85} index): $\frac{C_{AS} - C_{blank}}{C_{inj.} \times ml.\ injected}$. C_{AS} is the count per minute obtained from the arterial sample and $C_{inj.}$ the count per minute per milliliter of the injected solution.

For the detection of a left-to-right shunt the patient's expired air was directed across the face of a thin-window G-M tube† inserted into the expiratory line of the closed breathing circuit. The patient was usually instructed to hyperventilate for several seconds after the injection to decrease the time interval required for the gas to traverse the tracheobronchial tree. The output of the tube was integrated by a count-rate meter and recorded continuously on a direct-writing oscillograph.

*Model M-4, Nucleonic Corporation of America, New York, N. Y.

†Model TCG-2, Tracerlab-Keleket, Waltham, Mass.

In every patient the presence or absence of a shunt was verified by the findings at operation or autopsy or other diagnostic technics, including selective angiography, the results of nitrous oxide or Kr^{85} inhalation tests, and dye-dilution curves.

Results

In 19 patients Kr^{85} was injected into the right side of the heart or into the pulmonary artery, either in the absence of or distal to the origin of a right-to-left shunt. The ratio of the arterial blood radioactivity to the total radioactivity injected ranged from 0.0 to 9.0 $\times$ 10^{-5}, and the mean value was 2.5 $\pm$ 2.6 $\times$ 10^{-5} (fig. 1). Kr^{85} was injected into the right side of the heart proximal to the origin of a right-to-left shunt in 9 patients. Under these circumstances the ratio of the arterial blood activity to the total activity injected ranged from 8.2 $\times$ 10^{-5} to 81 $\times$ 10^{-5} with a mean of 30.1 $\pm$ 22.7 $\times$ 10^{-5} (fig. 1).

Injections were made into the left side of the heart proximal to the origin of a left-to-right shunt in 22 patients. The appearance time in the expired air ranged from 1.0 to 7.8 seconds, and the mean appearance time was 4.0 $\pm$ 1.6 seconds (fig. 2). The appearance times in expired air ranged from 1.0 to 6.0 seconds with a mean of 3.3 $\pm$ 1.5 seconds in the 17 patients in whom the Kr^{85} was injected into the right side of the heart or pulmonary artery. Kr^{85} was injected into the left side of the heart or aorta distal to the origin of a left-to-right shunt or in the absence of a shunt in 18 patients. The appearance time in expired air ranged from 6.5 to 33.0 seconds, with a mean of 15 $\pm$ 5.0 seconds (fig. 2). In 5 patients Kr^{85} was injected into the right heart or pulmonary artery as well as into the left side of the heart in the absence of, or distal to, the origin of the left-to-right shunt. The appearance time from the right-heart injection preceded that from the left-heart injection by 7 to 15 seconds, and the average difference was 10.8 $\pm$ 2.9 seconds. In 10 patients injections were made into the left side of the heart both proximal and distal to the origin of the left-to-right shunt. The appearance in expired air following the injections proximal to the origin of the shunt preceded the appearance following injections distal to the origin of the shunt by 3.0 to 16.5 seconds, with an average of 10.5 $\pm$ 4.9 seconds. The ascending limbs of the expired air curves were

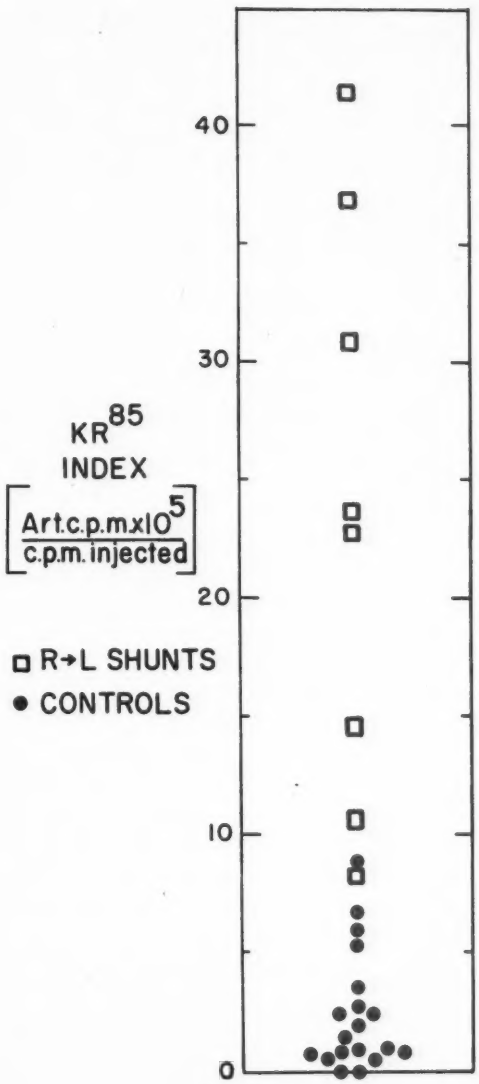

Figure 1

Arterial Kr^{85} indices determined following injections proximal to right-to-left shunts (open squares) *and either distal to them or in patients without shunts* (solid circles). *The highest index obtained (81) is not plotted.*

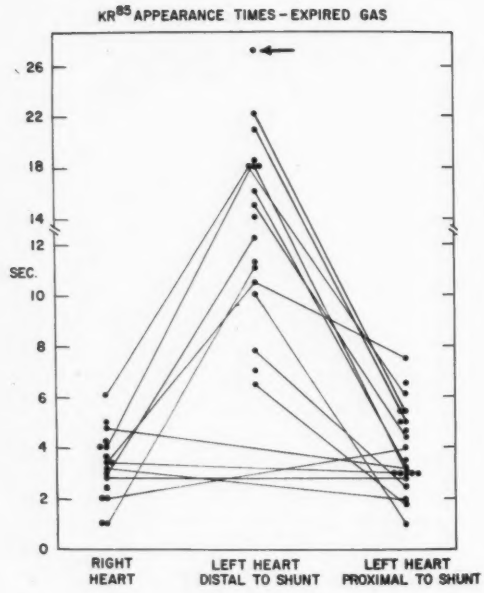

Figure 2

Appearance times of Kr^{85} in expired air following injections at various sites. Lines cannect multiple observations in the same patient. The arrow designates the highest value, which was 33 seconds.

generally steep when the injections were made into the right side of the heart or into the left side of the heart proximal to the origin of the left-to-right shunt. In contrast, the ascending limbs of the expired air curves were jections were made into the left heart distal to the origin of a shunt.

Illustrative Applications of the Methods

Case 1

W. M., a 46-year-old man with congenital heart disease and cyanosis was found at right heart catheterization to have a large left-to-right shunt at the atrial level. The right ventricular pressure was elevated but the pulmonary artery could not be entered. Injection of Kr^{85} solution into the inflow tract of the right ventricle yielded an arterial index of 5.8×10^{-5}, indicative of no venoarterial shunt originating at, or distal to, the right ventricle. Injection into the right atrium, however, yielded an index of 81×10^{-5}, clearly proving a large right-to-left shunt across the interatrial septum. Total anomalous pulmonary venous drainage into the right atrium and the associated atrial septal defect were corrected at open operation. Thus, in this cyanotic patient the normally low arterial level recorded following right ventricular injection localized the origin of the shunt to a level proximal to the competent tricuspid valve.

Case 2

E. H., a 5-year-old boy had been mildly cyanotic and had had a heart murmur since birth. At right heart catheterization the catheter crossed the interatrial septum and the right atrial nitrous oxide test was 25 per cent,[8] indicative of a small left-to-right shunt at this level. The catheter entered a posterior ventricular chamber where the systolic pressure was markedly elevated and near systemic arterial systolic pressure; it could not be advanced into the pulmonary artery or aorta. After injection of 30 μc. of Kr^{85} into this ventricle the arterial index was found to be only 1.0×10^{-5}, indicating that the entire outflow from this ventricle perfused the lungs and identifying it as the right ventricle. A selective angiocardiogram with the catheter in this position confirmed that it was the right ventricle and demonstrated dextroversion of the heart with valvular pulmonary stenosis. The ventricular septum was intact.

In many patients with right ventricular hypertension, proper identification of the ventricle or great vessel entered by the catheter may be difficult. While the appearance times of injected dye may be helpful,[9] these studies may be inconclusive, particularly in children with an extremely brief pulmonary transit time. The drainage path or paths of a cardiac chamber may be readily determined if the appearance of the isotope in expired air is monitored and its level in arterial blood is also determined. In this patient the very low level of the gas in arterial blood proved that the entire output of the ventricle perfused the lungs and by exclusion localized the right-to-left shunt responsible for the cyanosis to the atrial level.

Case 3

L. B., a 22-year-old laborer had the clinical findings of persistent atrioventricular canal. At catheterization a large left-to-right shunt entered the right atrium and the catheter easily crossed the interatrial septum and entered the left atrium and left ventricle. In order to determine whether left ventricular blood contributed to the shunt, both cardio-green dye and Kr^{85} injections were made into the left ventricle. The dye was detected in brachial arterial blood by technics previously described,[10] and the appearance and concentration of Kr^{85} were recorded in expired air (fig. 3). It was difficult to determine from the contour of the descending limb of the dye curve[10] whether or not a small shunt from the ventricle was present. The prompt appearance (2.5 seconds) of Kr^{85} in the expired air, however, clearly proved that left ven-

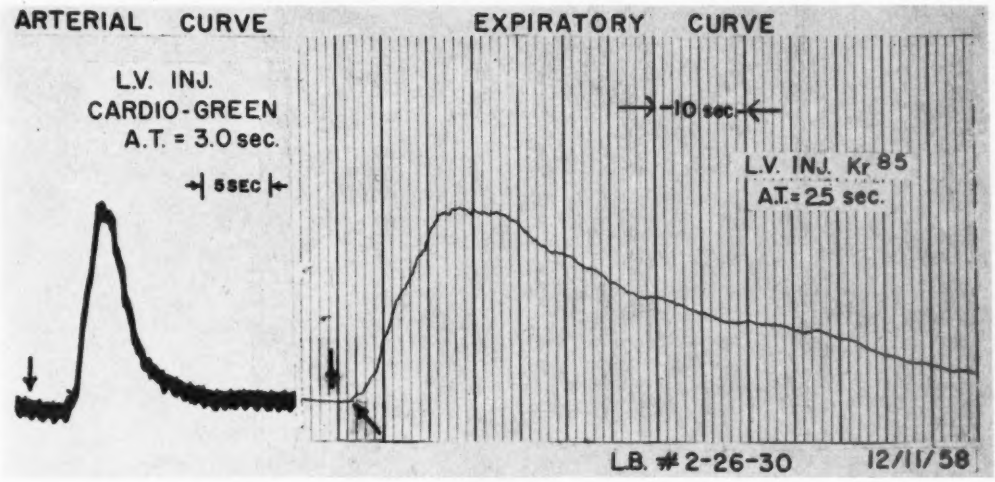

Figure 3

Indicator-dilution curve (brachial artery sampling) and expiratory Kr^{85} curve obtained after left ventricular injections in a patient with complete A-V canal. The dye curve is not diagnostic but the Kr^{85} curve establishes the presence of a shunt originating from the left ventricle. Vertical arrows indicate midpoint of injection. A. T. represents appearance time.

tricular blood passed to the pulmonary artery. At operation a complete form of persistent atrioventricular canal was found with both interatrial and interventricular communications.

Case 4

R. T., a 24-year-old man, was thought to have an atrial septal defect of the usual type. Right heart catheterization was performed through the saphenous vein, and a large left-to-right shunt was found at the atrial level, the nitrous oxide index in the right atrium being 69 per cent. The catheter was passed through the atrial defect into the left atrium and left ventricle. Kr^{85} injected into the left ventricle appeared in expired air in 18 seconds. The catheter tip was then withdrawn into the left atrium and a Kr^{85} injection then resulted in an appearance time of 3 seconds. These findings localized the origin of the left-to-right shunt to the left atrium and proved that left ventricular blood did not contribute to it. These findings lent support to the diagnosis of an ostium secundum atrial septal defect. This lesion was demonstrated and repaired at operation.

Case 5

A. R., a 17-year-old student, was intensely cyanotic and only a single sound was audible at the base of the heart and only a soft precordial systolic murmur was present. When operation was planned, the differentiation of tetralogy of Fallot from pulmonary atresia or truncus arteriosus became necessary. The right ventricular systolic pressure was equal to the systemic and although the catheter easily entered the aorta it could not be passed into the pulmonary artery. Kr^{85} appeared in expired air 6 seconds after right ventricular injection, and the concentration rose abruptly. An injection in the aortic arch gave an identical appearance time, but Kr^{85} injected into the abdominal aorta appeared in expired air only after 18 seconds and in low concentration (fig. 4). Indicator-dilution curves from all these sites were similar and resembled normal curves after left ventricular injection, demonstrating no evidence of pulmonary blood flow. The early appearance of Kr^{85} after injection into both the thoracic aorta and right ventricle indicated that blood from the aorta perfused the lungs. Selective angiography and subsequent operation proved the lesion to be pulmonary atresia and that the pulmonary flow originated from dilated bronchial arteries.

Case 6

A. R., a 42-year-old housewife, presented the classic findings of patent ductus arteriosus. The pulmonary artery nitrous oxide test was 39 per cent. At operation, a ductus 8 mm. in diameter was isolated and occluded with a Blalock clamp. Injections of a mixture of Kr^{85} and cardio-green dye were then made into the left atrium, as the gas was monitored in expired air, and dye curves were recorded from the brachial artery. Following in-

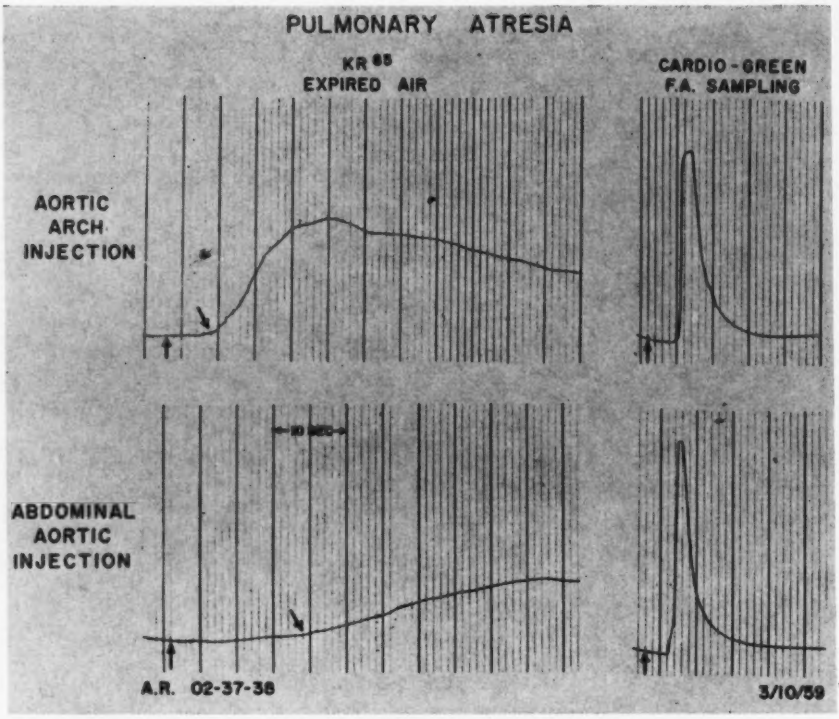

Figure 4

Expiratory Kr^{85} curves and indicator-dilution curves recorded after aortic injections in a patient with pulmonary atresia. The difference in Kr^{85} curves proves that the origin of the pulmonary blood flow is from the thoracic aorta. Vertical arrows indicate midpoint of injection and oblique arrows appearance time.

jections with the ductus closed, the clamp was opened until a faint systolic thrill was palpable in the main pulmonary artery and the injections were repeated. The contours of the dye curves (fig. 5) were similar but the appearance time of Kr^{85} was 11 seconds earlier when the tiny shunt was functioning.

Discussion

The injection of Kr^{85} solution into the cardiac chambers and great vessels and its subsequent detection in arterial blood and expired air provides another sensitive and convenient method for the detection and localization of circulatory shunts. The small amounts of Kr^{85} employed and its extremely brief biologic half-life make its use safe for both the patient and laboratory personnel.

When K^{85} in solution is injected into the circulation, it does not act as a simple intravascular indicator such as Evans blue or tricarbocyanine. The gas is soluble and diffuses freely into the extracellular and intracellular spaces and thus is delayed in its passage through the systemic circulation. Similarly, Kr^{85} easily crosses the alveolar capillary membrane and 95 per cent of it is eliminated from blood by 1 passage through the pulmonary circulation.[3] These properties of the isotope make it particularly suitable in studies such as those described, as well as in the detection of valvular regurgitation[11] and portal-systemic venous communications.[12]

In the detection of left-to-right shunts the appearance time of Kr^{85} in expired air after its injection into the left side of the heart is apparently a more sensitive method than indicator-dilution curves recorded from a systemic artery after either right or left heart injection (figs. 3, 4, and 5). This advantage relates

to the fact that a finite point, the appearance time of the gas, is utilized rather than an analysis of the contour of a time-concentration curve. In some instances, however, it may be necessary to compare appearance times from various injection sites to determine whether a shunt is present, since the normal systemic and pulmonary circulation times vary widely from patient to patient (fig. 2); the size of the patient and the degree of compensation are, of course, important determinants. If the appearance time is between 6 and 8 seconds, the area of overlap, a more proximal left heart injection or a right heart injection will indicate the diagnostic significance of the original value. No comparison has as yet been made of the relative accuracy of the Kr^{85} injection method with indicator-dilution curves recorded from the right heart after left heart,[13] pulmonary arterial,[14] or intravenous injection.[15] These latter technics have definite advantages over arterial dilution curves but may require the insertion of 2 catheters.

For the detection of right-to-left shunts integrated samples of arterial blood were counted. Although shunts could be detected and localized with this technic, time concentration curves of the isotope in arterial blood will undoubtedly prove to be superior. In the present study no effort was made to calculate the magnitudes of right-to-left shunts, but this may conveniently be done by appropriate application of the Stewart-Hamilton formula.[16] F = systemic flow (ml./sec.), i = total radioactivity injected (cts./min.), t = sampling period (sec.) and c = the mean arterial concentration of Kr^{85} during the sampling period (cts./min./ml.) The formula is usually expressed as:

1. $F = i/ct.$; rearranging,

2. $c = i/Ft$; c may be calculated ($C_{calc.}$) if it is assumed that none of the Kr^{85} injected in the right heart is cleared by the lungs and the sampling time embraces the entire dilution curve. The magnitude of the shunt may be estimated by relating the counts observed ($C_{obs.}$) to the calculated value ($C_{calc.}$). Correction must be made in $C_{obs.}$ for the small portion of the isotope that normally appears in arterial blood ($C_{nor.}$).

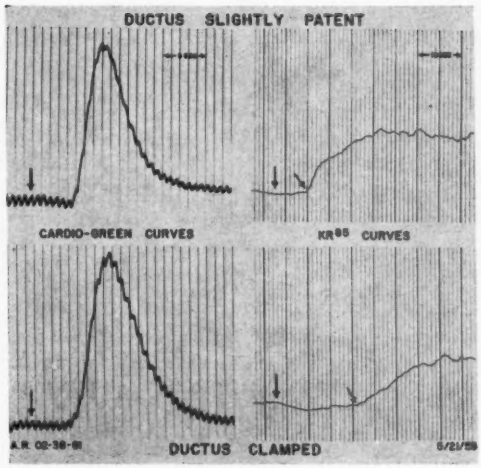

Figure 5

Indicator-dilution curves (brachial artery samples) and expiratory Kr^{85} curves recorded after simultaneous injections into the left atrium of a patient with a patent ductus.

3. $C_{nor.}$ is dependent upon the total amount of Kr^{85} injected and if $C_{nor.}/i$ is assumed to be constant, $C_{nor.}$ may be determined by an injection distal to the origin of the shunt, or an average for this value may be calculated from the data in control injections shown in figure 1. This average value was found to be $2.5 \times 10^{-5} \times i$.

Thus, the right-to-left shunt (fraction of systemic venous return bypassing the lungs) $= \dfrac{C_{obs.} - C_{nor.}}{C_{calc.}}$

The data obtained in patient W. M. above may be analyzed in this manner. The systemic flow (Fick) was 4.2 L./min. (70 ml./sec.) and 1.3×10^6 counts per minute were injected each time (i). The arterial count after right ventricular injection ($C_{nor.}$) was 75 cts./min./ml. and after right atrial injection ($C_{obs.}$) was 1045 cts./min./ml. $C_{calc.} = \dfrac{1.3 \times 10^6}{7 \times 10^1 \times 1.5 \times 10^1} = 1240$ cts./min./ml.

$$\textit{Right-to-left shunt} = \frac{1045 - 75}{1240} = 78\%$$

Summary

Following injection of krypton^{85} in solution into the right side of the heart, approximately 95 per cent is cleared during 1 passage through the pulmonary circulation. Arterial blood activity is low when radioactive Kr^{85} is injected in the absence of, or distal to, the origin of a right-to-left shunt. However, when injected proximal to the origin of such a shunt, a fraction of the Kr^{85} bypasses the pulmonary capillary bed and appears in arterial blood. Thirty to 50 μc. Kr^{85} were injected into the right heart, and arterial blood was sampled during the next 15 seconds. In 19 patients without right-to-left shunts, the activity per milliliter of arterial blood was always less than 9.0×10^{-5} and averaged $2.5 \pm 2.6 \times 10^{-5}$ of the total radioactivity injected. In 9 patients with proved right-to-left shunts, the radioactivity per milliliter of arterial blood always exceeded 8.2×10^{-5} and averaged $30.1 \pm 12.2 \times 10^{-5}$ of the total activity injected. By appropriate rearrangement of the Stewart-Hamilton formula the data permit calculation of the magnitude of the right-to-left shunt.

Following injection into the left heart, proximal to the origin of a left-to-right shunt, Kr^{85} promptly arrives in the pulmonary vascular bed and immediately appears in the expired gas, where it may be readily detected. In 22 such patients Kr^{85} appeared in the expired gas in an average of 4.0 ± 1.6 seconds. However, after injection distal to the origin of a left-to-right shunt in 18 patients, the appearance of Kr^{85} in the expired gas was delayed to a mean of 15.0 ± 5.0 seconds.

The technics described are convenient, simple to apply during cardiac catheterization, and sufficiently sensitive to detect and localize even small cardiac shunts.

Summario in Interlingua

Post le injection de krypton radioactive in forma de solution a in le latere dextere del corde, approximativemente 95 pro cento es eliminate in le curso de un sol passage per le circulation pulmonar. Le radioactivitate in sanguine arterial es basse quando le Kr^{85} es injicite in le absentia de un derivation dextero-sinistre o quando in le presentia de un tal le injection es effectuate a un puncto distal con respecto a su origine. Tamen, quando le injection es effectuate a un puncto proximal con respecto al origine de un derivation dextero-sinistre, un fraction del Kr^{85} evita le vasculatura pulmono-capillar e appare in le sanguine arterial. Inter 30 e 50 μc de Kr^{85} esseva injicite in le corde dextere, e specimens de sanguine arterial esseva obtenite durante le sequente 15 secundas. In 19 patientes sin derivationes dextero-sinistre, le activitate per millilitro de sanguine arterial esseva semper minus que $9{,}0 \times 10^{-5}$ con un valor medie de $2{,}5 \pm 2{,}6 \times 10^{-5}$ del quantitate total de radioactivitate injicite. In 9 patientes con demonstrate derivationes dextero-sinistre, le radioactivitate per millilitro de sanguine arterial excedeva semper $8{,}2 \times 10^{-5}$, con un valor medie de $30{,}1 \pm 12{,}2 \times 10^{-5}$ del quantitate total de activitate injicite. Per medio de un appropriate re-arrangiamento del formula de Stewart-Hamilton, le datos permitte le calculation del magnitude del derivation dextero-sinistre.

Post injectiones in le corde sinistre, proximal al origine de un derivation sinistro-dextere, Kr^{85} arriva promptemente in le vasculatura pulmonar e appare immediatemente in le expiration ubi illo es facile a deteger. In 22 tal patientes, Kr^{85} appareva in le gas del expiration intra $4{,}0 \pm 1{,}6$ secundas. Tamen, post-injectiones distal con respecto al origine del derivation sinistro-dextere, le apparition de Kr^{85} in le del expiration, studiate in 18 tal patientes, occurreva solmente post $15{,}0 \pm 5{,}0$ secundas.

Le technicas describite es convenibile, simple a applicar in le curso de catheterismo cardiac, e sufficientemente sensibile pro le detection e localisation de mesmo micre derivationes cardiac.

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Jaenike, J. R., and Waterhouse, C.: Body Fluid Alterations During the Development of and Recovery from Hyponatremia in Heart Failure. Am. J. Med. **26**: 862 (June), 1959.

Metabolic studies are reported on patients with advanced cardiac disease and congestive failure during the development of hyponatremia and during the restoration of a normal serum sodium concentration. While hospitalized in a metabolic ward, measurements of water, sodium, potassium, chloride, and nitrogen balance were made. The results indicated that abnormalities both in external excretion and internal distribution of water and electrolytes exist in these patients, either of which may be the predominant factor in the pathogenesis of this syndrome. For example, a loss of water in excess of fixed cation accounted for the correction of hyponatremia in certain subjects. In others, primary water retention, leading to dilution of body fluids, was responsible for hyponatremia. In still others, this was due to internal redistribution of electrolyte.

Rinzler

Some Circulatory Effects of 5-Hydroxytryptamine in Man

By P. Harris, M.D., H. W. Fritts, Jr., M.D., and A. Cournand, M.D.

VASOACTIVE drugs have in general proved to have much weaker effects on the pulmonary circulation than on the systemic circulation. However, 5-hydroxytryptamine (5-HT) has been thought to be an exception because it causes a distinctive rise in the pulmonary vascular resistance both in intact animals[1-6] and in perfused lungs.[7-10] Since this substance circulates in the human body, the possibility arises that 5-HT might control the pulmonary vascular resistance—a possibility strengthened by the observation that the concentration of the agent diminishes during its passage through the pulmonary vessels.[7] In the present study, this hypothesis was tested in 10 patients with normal hearts and minimal healed tuberculous lesions of the lungs.

Methods

5-HT was given in the form of the creatinine sulfate salt dissolved in 0.9 per cent saline. The doses specified in table 1 have been expressed in terms of 5-HT base.

All of the subjects were in a fasting and basal state, and all were studied in the supine position. In 7 subjects the effects of continuous infusions of 5-HT were observed. For this purpose a double-lumen catheter with only 5-cm. distance between the openings was advanced until the proximal opening lay in the main pulmonary artery just beyond the pulmonic valve. 5-HT was administered by a constant-infusion pump via the side opening of the catheter, while measurements of pressure and samples of blood were obtained from the opening at the end. An indwelling needle in the right brachial artery provided a means of obtaining blood samples and measuring pressures in the systemic circulation.

The patient breathed air through a mouthpiece connected to an open breathing circuit. The pressures in the pulmonary and brachial arteries were measured 6, 8, and 10 minutes after the mouthpiece was inserted, and the cardiac output was measured by the Fick principle at the end of the ninth minute. Two minutes later, the infusion of 5-HT was started. The pressures were measured after 2 and 4 minutes of infusion, and the cardiac output was measured after 5 minutes. The infusion was then stopped and in most of the patients after 3 minutes the pressures were measured again.

In 3 subjects, doses of 5-HT of 1, 2, and 4 μg. per Kg. were rapidly injected into the right atrium through a cardiac catheter. In these subjects a second catheter was placed in the pulmonary artery and the pressures in the pulmonary and brachial arteries were recorded during the injection.

Results

The results of the continuous infusions of 5-HT are presented in tables 1 and 2. Only 1 subject (M.M.) showed an unequivocal rise in pressure in the pulmonary artery during the infusion, which was accompanied by a rise in brachial arterial pressure. In another subject (L.Z.) there was some rise in both pulmonary and systemic arterial pressures during the second infusion. The most frequent response was a rise in pulse rate. There was no consistent alteration of cardiac output, ventilation, or arterial oxygen saturation. The oxygen uptake showed considerable variation; the respiratory quotient showed little change.

The single rapid injections of 1 and 2 μg. per Kg. of 5-HT base into the right atrium of 2 subjects caused no alteration in the pressure in the pulmonary or brachial arteries. The rapid injection of 4 μg. per Kg. into the right atrium of the third subject had such profound effects that the study was discontinued (fig. 1.).

Five seconds after injection, the subject started to cough. Between the ninth and twelfth seconds after the injection, there was no ventricular complex on the electrocardiogram and the pressure in both the brachial and pulmonary arteries fell greatly. During this 3-second interval, however, 1 P wave was

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Supported by a research grant (H-2001 (C)) from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.

Table 1

*Effects of an Intravenous Infusion of 5-Hydroxytryptamine (5-HT) on the Circulation in Seven Human Subjects**

Case	Dose of 5-HT (μg./Kg./min.)	Time	PA (mm. Hg)	BA (mm. Hg)	HR	$\dot{Q}$ (L./min./M.²)
			s/d,m	s/d,m		
H.R.	2.4	Before	24/6,14	139/82,105	54	3.2
		During	24/7,13	137/81,106	59	4.2
T.B.	3.0	Before	17/7,10	138/93,111	118	3.3
		During	16/7,10	136/92,110	122	4.2
		After	14/5,8	137/95,112	121	
M.M.	4.5	Before	27/12,18	128/75,98	71	3.5
		During	33/17,23	158/91,112	73	3.5
T.H.	4.5	Before	35/13,22	146/88,119	60	3.1
		During	34/13,22	152/92,121	73	4.5
		After	32/11,21	153/91,122	75	
W.M.	6.5	Before	20/8,13	126/78,99	94	4.9
		During	20/9,14	126/78,99	102	5.4
		After	22/9,14	131/79,100	99	
L.Z.	1.85	Before	18/4,11	114/67,88	65	2.8
		During	15/3,9	114/67,86	74	2.7
	3.7	Before	14/2,9	93/55,73	71	2.7
		During	18/4,12	107/68,87	74	2.9
		After	18/4,11	102/64,83	70	
J.S.	4.5	Before	19/6,12	138/75,101	93	4.5
		During	17/8,12	136/79,103	102	4.9
		After	18/9,13	130/75,99	89	
	5.5	Before	18/7,12	133/78,101	84	4.4
		During	21/8,13	132/78,103	98	4.2
		After	20/6,12	132/77,100	86	

*The symbols used in tables 1 and 2 are defined as follows[23]: PA, pulmonary arterial pressure; BA, brachial arterial pressure; HR, heart rate; $\dot{Q}$, cardiac output; $\dot{V}_E$, volume of gas expired per minute (BTPS); $\dot{V}_{O_2}$, volume of oxygen taken up per minute (STPD); R_E, respiratory exchange ratio; Ca_{O_2}, arterial blood oxygen content; $C\bar{v}_{O_2}$, mixed venous blood oxygen content; Sa_{O_2}, arterial blood oxygen saturation; CAP_{O_2}, arterial blood oxygen capacity.

recorded, which was associated with a pressure wave in the brachial and pulmonary arterial tracings. The period of asystole was followed by bradycardia, which gave way to a tachycardia by the twentieth second after the injection. By this time, the pulmonary arterial pressure had risen to a figure of 27/16 mm. Hg from a control value of 19/8 mm. Hg and the pressure in the brachial artery had risen to such an extent that only the diastolic value was recorded. During the succeeding 4 minutes these pressures gradually returned to their normal values.

Discussion

The normal rate of excretion of 5-hydroxyindoleacetic acid in the urine is said to be 2-9 mg. per day,[11] while patients with malignant carcinoid may excrete up to 900 mg. per day. If the excretion is taken as a measure of the average rate of production of 5-HT in the body, it will be seen that the rates of infusion of 5-HT into the circulation in this present study were greatly in excess of its average physiologic rate of production but within the range found under pathologic conditions.

At this rate of infusion, there was no con-

Table 2

Effects of an Intravenous Infusion of 5-Hydroxytryptamine (5-HT) upon the Ventilation and Respiratory Gas Exchange in Seven Human Subjects

Case	Time	$\dot{V}_E$ (L./min./M.²)	$\dot{V}_{O_2}$ (ml./min./M.²)	R_E	Cao_2 (ml./100 ml.)	$\bar{C}vo_2$ (ml./100 ml.)	Sao_2 (%)	$CAPo_2$ (ml./100 ml.)
H.R.	Before	6.4	114	.83	16.2	12.5	91	18.2
	During	10.0	144	.95	16.4	13.0	91	
T.B.	Before	4.3	136	.74	16.0	11.9	97	16.9
	During	5.4	166	.77	15.8	11.9	97	
M.M.	Before	5.3	134	.83	14.5	10.7	94	15.8
	During	5.0	131	.81	14.4	10.7	93	
T.H.	Before	3.9	145	.84	18.7	14.1	97	19.7
	During	4.7	144	1.03	18.8	15.5	98	
W.M.	Before	5.0	147	.84	15.5	12.5	97	16.6
	During	5.6	174	.81	15.7	12.5	97	
L.Z.	Before	4.0	122	.76	17.1	12.7	97	18.1
	During	3.7	105	.85	17.1	13.2	96	
	Before	4.3	120	.83	16.6	12.1	96	
	During	3.9	104	.89	16.2	12.6	93	
J.S.	Before	5.3	149	.84	18.3	15.0	97	19.4
	During	5.7	161	.87	18.3	15.0	97	
	Before	5.5	157	.86	17.8	14.2	94	
	During	5.2	147	.83	17.8	14.3	94	

sistent effect on the pressures in the pulmonary or brachial artery. The one time unequivocal changes in pressure were recorded, they were observed both in the pulmonary and brachial arteries. We were not able, therefore, to find a dosage of the drug that would influence the pulmonary arterial pressure without altering the brachial arterial pressure. Although the rise in pulmonary artery pressure in subject M.M. was not accompanied by any change in cardiac output, it is not permissible to assume that it was due to an increased pulmonary vascular resistance in the absence of any knowledge of the left atrial pressure. This is more particularly so, since there was evidence of systemic vasoconstriction that might have displaced blood from the systemic to the pulmonary circulation.

Of the other functions measured, the constant infusion of 5-HT caused no consistent change in cardiac output, arterial oxygen saturation, or ventilation. The only consistent finding was that the heart beat a little more rapidly during the infusion.

These observations are different from those made by Rudolph and Paul,[5] who studied the effects of sustained infusion of 5-HT in dogs. These authors found a 2- to 3-fold rise in the pulmonary arterial pressure with an eventual lowering of the systemic arterial pressure and a consistent rise in cardiac output averaging 60 per cent. The doses used by Rudolph and Paul were considerably greater than those used in these studies, the lowest rate of infusion being 9 μg. per Kg. per minute, the usual being 65 μg. per Kg. per minute of 5-HT base. Borst, Berglund, and McGregor,[9] however, infused 5-HT into 1 branch of the pulmonary artery in dogs at a rate of 1 to 14.6 μg. of base per Kg. per minute and found unequivocal evidence of an increased vascular resistance in the lung to which the drug had been given at all levels of dosage. These observations suggest that there is a species difference in the response to this substance.

Whether this difference lies in the responsiveness of the pulmonary arteries has now become doubtful since the work of Kniseley, Wallace, and Addison,[12] which appeared after our studies were completed. These authors showed by direct observation that the increased pulmonary vascular resistance ob-

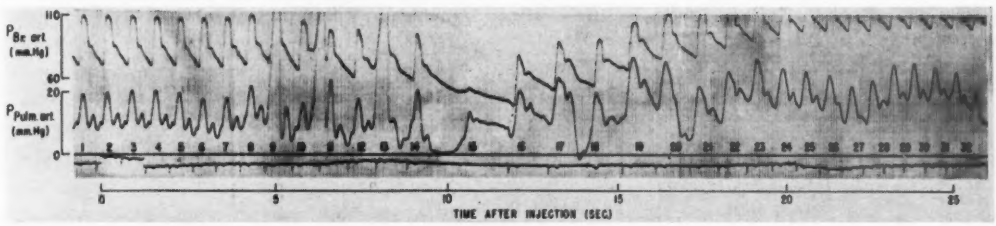

Figure 1

Effect of a rapid injection of serotonin on brachial arterial (BA) and pulmonary arterial (PA) pressures. For discussion, see text.

served following the intravenous injection of 5-HT in rabbits, cats, and dogs was associated with the lodging of many small emboli in the pulmonary arteries. The material composing the emboli soon broke up and passed through the capillaries, after which the pulmonary vascular resistance returned to normal. The action of 5-HT may therefore be primarily or entirely a mechanical one, and the difference between dogs and men may lie in the chemical composition of the blood rather than in the medial musculature of the pulmonary arteries. The lack of effect of infusions of 5-HT on the human pulmonary circulation is consistent with the absence of pulmonary hypertension in patients with malignant carcinoid.[13, 14]

As far as the systemic circulation is concerned, Page and McCubbin[15] found, like Rudolph and Paul,[5] that the effect of a continuous intravenous infusion of 5-HT in dogs and cats was usually a sustained lowering of arterial pressure. In neurogenic hypertensive dogs this hypotensive effect was more evident, whereas, in normal dogs that had received ganglion-blocking agents, 5-HT caused a rise in arterial pressure. By these and other experiments,[16] these authors distinguished between a direct action of 5-HT on the arterial vessels, which caused constriction, and an indirect vasodilator action of the drug due to its property of decreasing neurogenic tone. In patients with benign hypertension, however, sustained intraveous infusions of 5-HT at rates of 0.2 to 1.5 mg./min. raised the systemic arterial pressure.[15] Magalini, Stefanini, and Smith[17] infused 5-HT at a rate of 144 μg. base/min. for 30 minutes into a peripheral vein of 1 human subject and observed local venoconstriction but no alteration in the systemic arterial blood pressure. Similar results were obtained by Hollander, Michelson, and Wilkins[18] with the intravenous infusion of 4.4 to 21.7 μg. of 5-HT base per minute. Spies and Stone[19] injected 5-HT intravenously into human subjects in doses of 0.1 to 2.2 mg. of base given over 5 to 300 seconds. Whenever more than 217 μg. of base was injected, systolic arterial blood pressure as measured by a cuff-sphygmomanometer rose. These doses also caused pains in the abdomen and other sensations that were absent in our subjects. The effects of arterial infusion of 5-HT have been studied by Haddy, Fleischman, and Emanuel[21] in the isolated foreleg of the dog. Large arteries and veins constricted but small vessels dilated, the total vascular resistance not being substantially altered. Roddie, Shepherd, and Whelan[20] found that the infusion of 0.11 to 7 μg. of 5-HT base per minute into the brachial artery in man caused a fall in blood flow through the forearm and hand and a flushing of the skin.

The mechanism underlying the tachycardia observed in our subjects is not clear. It is tempting to attribute such an effect to an alteration of the sensitivity of the baroreceptors of the carotid sinus due to the local action of 5-HT. There is little experimental evidence in favor of such an action, however, except for a report by Gordon, Haddy, and Lipton,[22] that during the infusion of 5-HT, norepinephrine causes a tachycardia instead of the usual bradycardia.

In animals, a qualitative difference has been found between the effects of short intravenous injections and of continuous infusions of

5-HT.[15, 16] A single injection is followed by a rapid rise in the pulmonary arterial pressure.[1-7] The response of the systemic arterial pressure is more complex. Working with vagotomized cats under chloralose, Reid[1] found that the intravenous injection of 5-HT caused an initial fall in the systemic arterial pressure followed by a rise and then a prolonged fall. The initial fall in systemic arterial pressure coincided with the rise in pulmonary arterial pressure and fall in left atrial pressure. After injection into a pulmonary vein, the initial fall in systemic arterial pressure was absent and the rise in pulmonary arterial pressure was slight and delayed. Reid therefore thought that the initial fall in systemic arterial pressure was caused by pulmonary vasoconstriction. Others[7] reached a similar conclusion.

Comroe et al.,[3] however, found that the rapid intravenous injection of 5-HT into cats with intact vagi under chloralose caused bradycardia, systemic hypotension, and apnea, such as is found in the Bezold reflex. In addition there was a rise in right ventricular pressure, which was interpreted as being due to pulmonary vasoconstriction. Atropine and vagotomy blocked the bradycardia and hypotension but did not influence rises in right ventricular and vena caval pressures. These authors found that the Bezold-like reflex could occur before the appearance time of tracer substances in the aorta. The same reflex could also be elicited, however, by injections into the left ventricle or ascending aorta; it was concluded that receptors were stimulated in both the pulmonary and the coronary circulation.

The sequence of events in figure 1 indicates that the initial fall in brachial arterial pressure was the first change to occur; its rapid time of appearance after injection might be construed as evidence of its reflex nature. The rise in pulmonary arterial pressure occurred later, when it was in fact accompanied by a rise in pressure in the brachial artery. This rise in pulmonary arterial pressure may have been due to a sustained increase in pulmonary vascular resistance or could have been caused by an increase in pulmonary blood volume arising from vasoconstriction in the systemic circulation. In this subject dilution curves of T 1824 injected into the right atrium may provide useful information about the mechanism underlying the cardiopulmonary events. In 3 such injections the average value for the appearance time of dye in the brachial artery was 7.5 seconds. Thus coughing, which started 5 seconds after the injection of 5-HT, presumably arose from receptors in the pulmonary circulation, while the bradycardia and hypotension, which appeared at 9 seconds, could have been caused by a reflex arising from receptors in the coronary circulation. There was no respiratory record in this study, but the pulmonary and brachial artery pressure tracings show coughing only between the fifth and eighth second. Whether apnea occurred at the time of ventricular arrest is not known, but immediately thereafter respiratory fluctuations could be seen on the pressure tracings. Hollander, Michelson, and Wilkins,[18] using rapid intravenous injections of 0.11 to 0.87 mg. of 5-HT base in man, noted a variable response in the systemic arterial pressure but nearly always a transient increase in the rate and depth of breathing. The pulmonary arterial pressure was not affected. They did not encounter any such alarming episode as occurred in our subject.

Summary

Continuous infusions of small quantities of 5-hydroxytryptamine (5-HT) were made into the pulmonary artery in 7 human subjects. In only 1 instance was there an unequivocal rise in pressure in the pulmonary artery and this was accompanied by a rise in brachial arterial pressure. The most consistent effect of the drug was to raise the heart rate. There was no effect on the cardiac output.

Single rapid injections of 5-HT were made into the right atrium in 3 other subjects. In 1 of these subjects the injection of 4 μg. per Kg. caused transient ventricular arrest and systemic hypotension followed by a sustained rise in pressure in the pulmonary and brachial arteries. The results of this study were thought to indicate the presence of a Bezold-like reflex. The rapid injection of 5-HT was therefore thought to be dangerous and the investigation was discontinued.

Summario in Interlingua

Continue infusiones de micre quantitates de 5-ydroxytriptamina (5-HT) esseva effectuate in le rteria pulmonar de 7 subjectos human. Un augmento nequivoc del tension pulmono-arterial esseva con-tatate post ille tractamento in solmente un del casos, hic le augmento del tension pulmono-arterial esseva ccompaniate de un augmento del tension brachio-rterial. Le plus uniforme effecto del droga esseva e facto que illo augmentava le frequentia cardiac. Nulle effecto super le rendimento cardiac esseva no-tate.

Simple injectiones rapide de 5-HT esseva effectuate n le atrio dextere de 3 altere subjectos. In 1, le lose de 4 μg per kg de peso corporee causava un ransiente arresto ventricular e hypotension systemic equite per un perdurative augmento del tension in le arterias pulmonar e brachial. Es opinate que le resultatos de iste studio indica le presentia de un reflexo del typo Bezold. Isto significarea que le in-jection rapide de 5-HT es periculose. Per consequente le investigation esseva interrumpite.

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Adams-Stokes Attacks due to Atrial and Ventricular Arrest, Treated by Vagotomy

By W. F. GREENWOOD, M.D., F.R.C.P. (Can.), W. E. COOPER, M.D., M.R.C.S. (Eng.), L.R.C.P. (Lond.), AND T. A. BAYLEY, M.D.

OVER a hundred years ago the discovery of the inductorium and its use as a stimulator permitted the Weber brothers to investigate the function of the vagus nerves by stimulating them. For many years it has been known that stimulation of the left vagus predominantly affects the atrioventricular (A-V) node, depressing conduction and leading to ventricular standstill due to failure of A-V conduction. Stimulation of the right vagus, on the other hand, predominantly affects the sinoatrial (S-A) node, suppressing impulse formation at the S-A node with ventricular standstill due to failure of impulse production.[1, 2] This knowledge has remained in the textbooks of physiology and has seldom seemed to have much clinical application.

In 1950, Dr. William Oille observed a patient who had suffered from recurrent syncope for 20 years or more, due to intermittent A-V block. Section of the vagus trunk in the neck was followed by complete and lasting freedom from syncope, at the expense of slight huskiness resulting from laryngeal paralysis.[3] This case was an example of recurrent syncope, due to recurrent A-V block cured by section of the left vagus nerve in the neck.

The case described here is an example of syncope due to recurrent sinoatrial arrest. The episodes of cardiac arrest ceased following section of the right vagus in the neck.

Case Report

This 34-year-old policeman had been a healthy person, able to do heavy work. For 20 years, since the age of 15, he had had recurrent episodes of paroxysmal tachycardia of which he was conscious, but which were never bothersome. In 1955 an electrocardiogram during an attack showed a regular tachycardia (fig. 1). It is uncertain whether this was supraventricular tachycardia with transient bundle-branch block or whether it arose below the A-V node. No P waves were visible in a 12-lead electrocardiogram and the QRS complexes were different from a record taken a few days later, when the tachycardia had ceased (fig. 2). At this time Digoxin, 0.25 mg. daily, was started which he continued to take because he thought the episodes of tachycardia were less frequent when he took this drug.

On April 18, 1958, after running up a few steps while on patrol, he fainted and recovered consciousness at the bottom of the stairs. His right arm and leg shook. He continued his patrol, but 10 minutes later had another short episode of unconsciousness. On being admitted to a hospital in Niagara Falls an electrocardiogram (fig. 3) was taken. There were many short periods of cardiac arrest, with complete cardiac standstill involving both atria and ventricles. The longest recorded was 17 seconds and was accompanied by loss of consciousness and a minor convulsion. Following asystole, the heart beat was often resumed by a sinus beat followed by ectopic beats, characteristic of delayed right ventricular activation, closely followed by a P wave. At times tachycardia at 150 per minute was present. At other times the rate was about 33 per minute (fig. 4). At times inverted P waves in lead II suggested that the focus of impulse formation was below the sinoatrial node. During one of these episodes of bradycardia, with inverted P waves in lead II, 1.8 mg. (1/37 grain) of atropine given intravenously over a half-hour period, did not affect the rate, although his vision became blurred, his mouth dry, and his pupils large.

Although he had only 3 attacks of unconsciousness, he had many short episodes of cardiac arrest, during which his pulse stopped for 5 to 8 seconds, his skin became momentarily bloodless, and he felt faint.

On examination he was moderately obese, but no other abnormality was noted. His heart was at

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Supported by National Health Grants Administration, Canada.

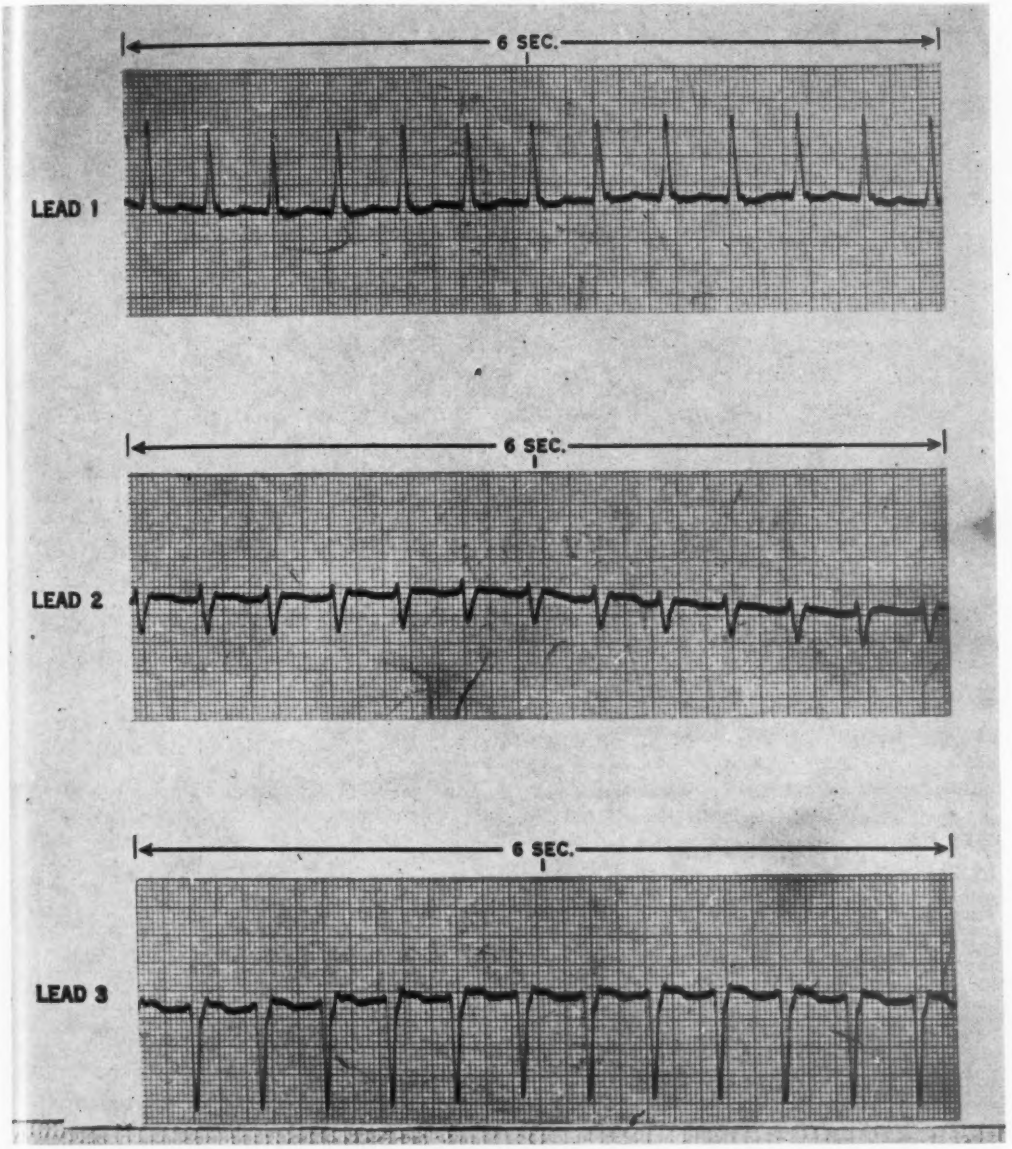

Figure 1

Electrocardiogram showed tachycardia, recorded in February 1955. It is uncertain whether this is supraventricular with bundle-branch block, or whether it arises below the atrioventricular node. No P waves were visible in any of the leads of a 12-lead electrocardiogram. (Courtesy of Dr. A. G. Minnes, Niagara Falls, Ontario.)

the upper limit of normal size on fluoroscopy. Protein-bound iodine estimation and uptake of radioactive iodine were normal. The serum electrolytes were normal.

Digoxin was stopped for 10 days, and efforts to control his symptoms with drugs were ineffective. Quinidine in doses of 0.2 Gm. 3 times a day led to diarrhea but had no other effect. Potassium chlo-

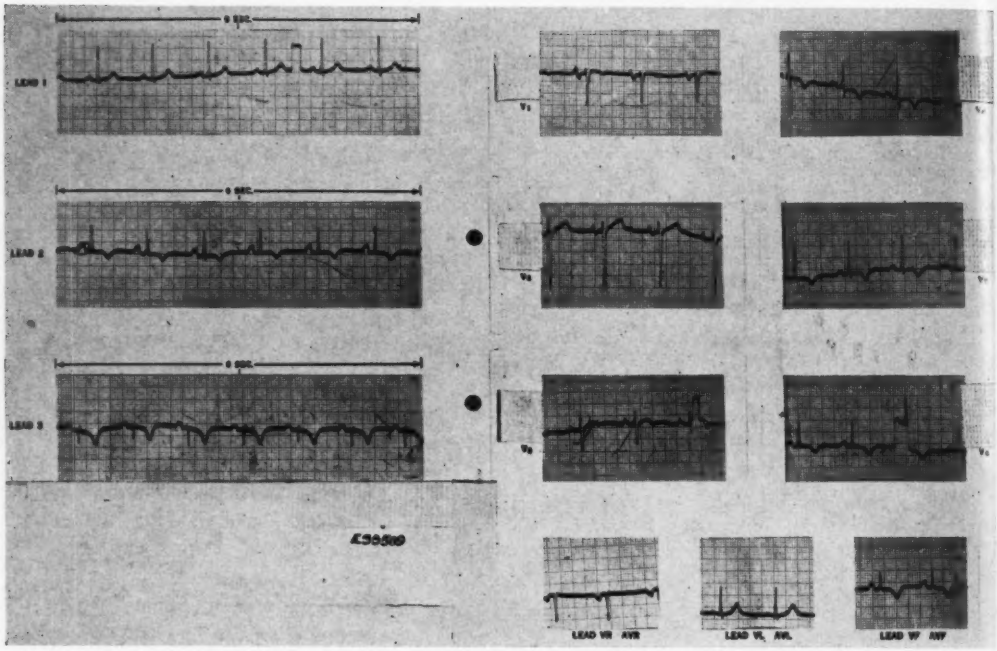

Figure 2

Electrocardiogram recorded February 5, 1955, showing sinus rhythm, with notched P waves and abnormal T Waves. (Courtesy of Dr. A. G. Minnes, Niagara Falls, Ontario.)

ride, procaine amide, isopropylnorepinephrine and phentolamine (Regitine) in the usual dosage had no effect. Atropine 0.9 mg. 5 times daily had no effect, and he would not tolerate more because of his dry mouth.

It seemed possible that intrinsic disease of the sinus node, which might be influenced by prednisone, might be responsible for the malfunction of the sinoatrial node. Consequently prednisone, 40 mg. a day, was started. He was not much different on this medication, but he was discharged for 3 weeks on 15 mg. daily. This medication had no effect, although he had an occasional day when he thought the episodes of cardiac arrest were less bothersome. When he was readmitted he had started to take Digoxin again, since he had a supply at home, and thought that it helped his episodes of tachycardia.

On August 15 Digoxin was stopped and he was given potassium chloride, 1 Gm., 3 times daily by mouth. Within 2 days the number of daily episodes of cardiac arrest, felt by the patient and heard with the stethoscope, decreased greatly. The electrocardiogram began to show a regular slow sinus rhythm, with upright P waves and normal QRS complexes at 38 to 60 beats per minute. The record was similar to that seen on February 5, 1955 (fig. 2). This slow sinus rhythm was present after the patient had been sleeping but when he was up and about he had a constant tachycardia, which varied from 112 to 184 beats per minute. The electrocardiogram was similar to that in figure 1. With a rate below 140 his blood pressure was 110-130/60-80, but at faster rates his blood pressure would fall to levels as low as 90/60-80, and he would feel uncomfortable and weak. He was unable to describe his discomfort in more detail. After August 19, 1958, no asystoles were heard. Carotid sinus pressure, eyeball pressure, changes in position, were repeated but again had no effect on the tachycardia.

On August 25, at 12 noon, under general anesthesia, Dr. R. O. Heimbecker isolated the right vagus high in the neck. A wire was put around the nerve and the wire was enclosed in a polyethylene tube, which extended beyond the skin, and through this tube was injected 1 ml. of 1 per cent procaine every hour, to keep the nerve paralyzed. During the procedure the patient had a constant tachycardia of 174 per minute, which was not changed by manipulation of the nerve. His rate remained rapid until 11:00 p.m. that evening, when it gradualy slowed down. Short periods of asystole of a few beats were noted on the electrocardiogram. By

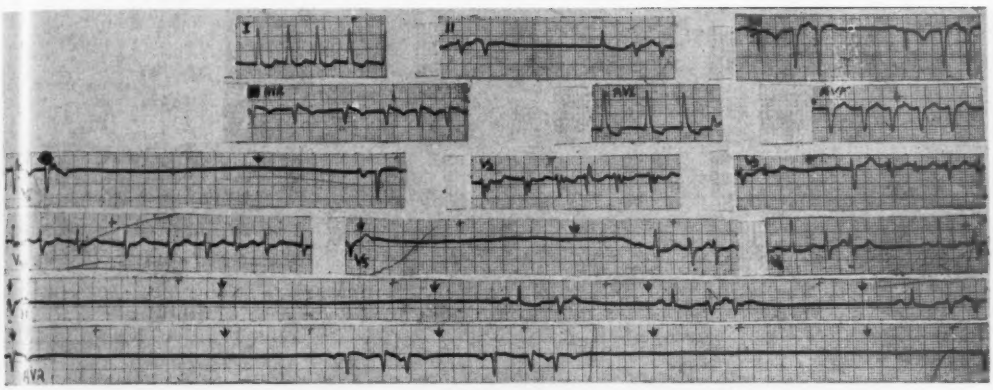

Figure 3

Electrocardiogram recorded April 18, 1958, showing episodes of sinoatrial arrest.

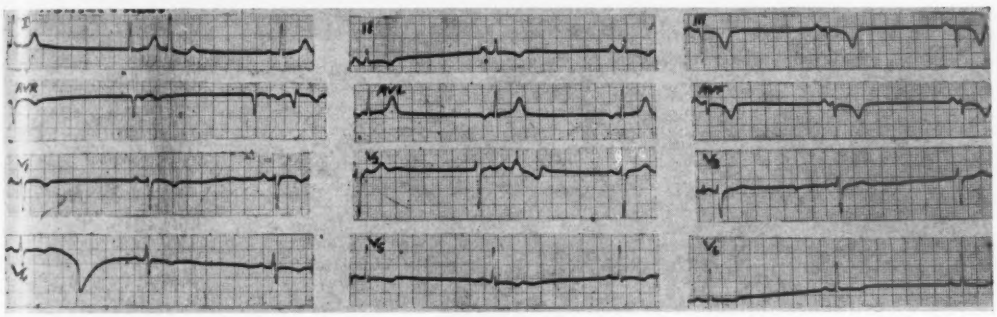

Figure 4

Electrocardiogram recorded April 19, 1958, showing sinus bradycardia. Rate about 33 per minute, with ectopic beats. In later records bradycardia was sometimes seen with inverted P waves in lead II.

12:00 midnight it had reverted to the regular slow sinus bradycardia at 55 to 60 per minute, with no asystole. Laryngoscopic examination confirmed that the nerve was at least partially anesthetized because the right vocal cord was partially paralyzed. The sinus bradycardia persisted most of the time, even when he was up and about, except for short periods on August 27 and August 28, when he had a tachycardia of 130 per minute.

On August 29, 1958, under general anesthesia, the vagus was cut by passing a current through the wire and withdrawing the wire. Before the operation he was emotionally upset. The tachycardia reappeared and persisted during the procedure. A few hours after the procedure the tachycardia reverted again to sinus bradycardia.

In 9 months since the operation there have been no more episodes of asystole. His voice is a little hoarse, due to the paralyzed vocal cord. He has had 4 or 5 episodes of tachycardia, particularly during periods of emotional stress. However, most of the time he is active, comfortable, and working. The last electrocardiogram was normal, except for notched P waves (fig. 5).

Discussion

This patient had recurrent episodes of cardiac arrest, during which no P waves were visible in the electrocardiogram. These were due either to failure of the sinoatrial node to produce impulses (sinoatrial arrest), or to failure of conduction of the electrical disturbance out of the node (sinoatrial block). To make a diagnosis of sinoatrial block, it is necessary to demonstrate that the periods of absent atrial activity are multiples of normal sinoatrial intervals.[4] When longer periods of cardiac arrest were occurring in this patient, the episodes of arrest were usually preceded by one or more ventricular or nodal ectopic

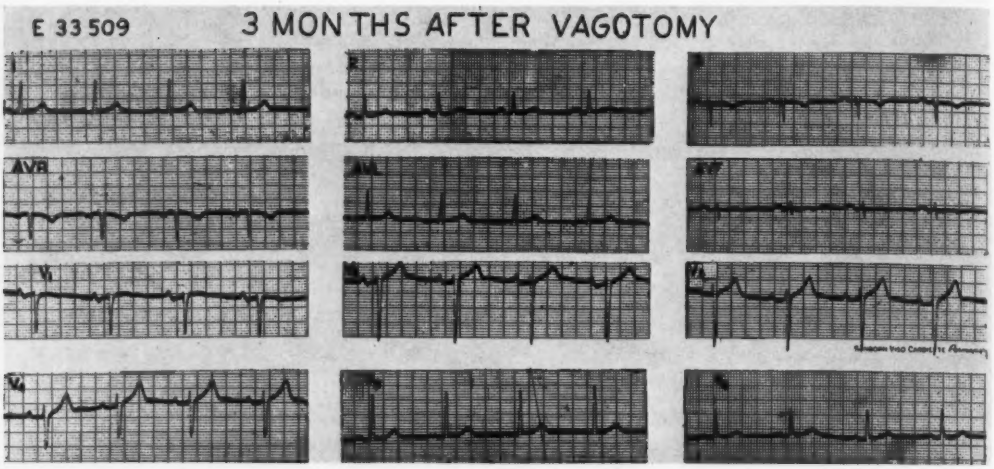

Figure 5

Electrocardiogram recorded December 1, 1958, about 3 months after vagotomy. The record is now normal except for the notched P waves.

beats. The P waves were so irregular, that one could not measure a regular interval between them (fig. 3). One record (fig. 6), in which the normal sinoatrial interval could be determined, showed sinus arrhythmia. In this record there are periods of arrest approximating 2 sinoatrial intervals, but the measurements of the P-P intervals are not sufficiently uniform to be certain of the mechanism of sinoatrial block.

When cardiac arrest occurred, at times an ectopic focus discharging at a rate slower than that of the normal sinoatrial node would take over the initiation of the heart beat. However, the ectopic focus would often discharge much more quickly than the sinoatrial node. This puzzling phenomenon has been observed in other similar patients,[5-7] but is not always present.[8, 9] It was usually impossible to say which came first: whether cardiac arrest was the first event, or whether in some way the rapid ectopic rhythm depressed the function of the sinoatrial node, leading to cardiac arrest when the ectopic rhythm stopped.

Hoff[2] has discussed a mechanism by which this rapid discharge may occur. During vagal stimulation, stimulation of the sympathetic nerves to the heart or the injection of epinephrine may produce ventricular extrasystoles that may have a more rapid rate than the sinoatrial nodal rhythm, which they displace. In this experimental situation vagal overactivity with suppression of the sinoatrial node was necessary before sympathetic stimulation could produce ectopic beats. Thus in our patient it seemed reasonable to consider interrupting the right vagus in the neck, to prevent the episodes of sinoatrial block. It seemed possible that this might also have some effect on the episodes of tachycardia. It may have been significant that emotional upsets, which could result in a sympathetic discharge or release of epinephrine, seemed important in precipitating tachycardia in this patient.

These theoretic considerations led us to advise vagotomy. Unfortunately this man was emotionally upset by his prolonged absence from work, as well as by the alarming sensation of having his heart stop repeatedly. He disliked doing without Digoxin, because it seemed to him to have been effective in the past in cutting down the frequency of episodes of tachycardia. When he was still having episodes of cardiac arrest, after 10 days without Digoxin, it seemed unlikely that omission of Digoxin would prevent the episodes of cardiac

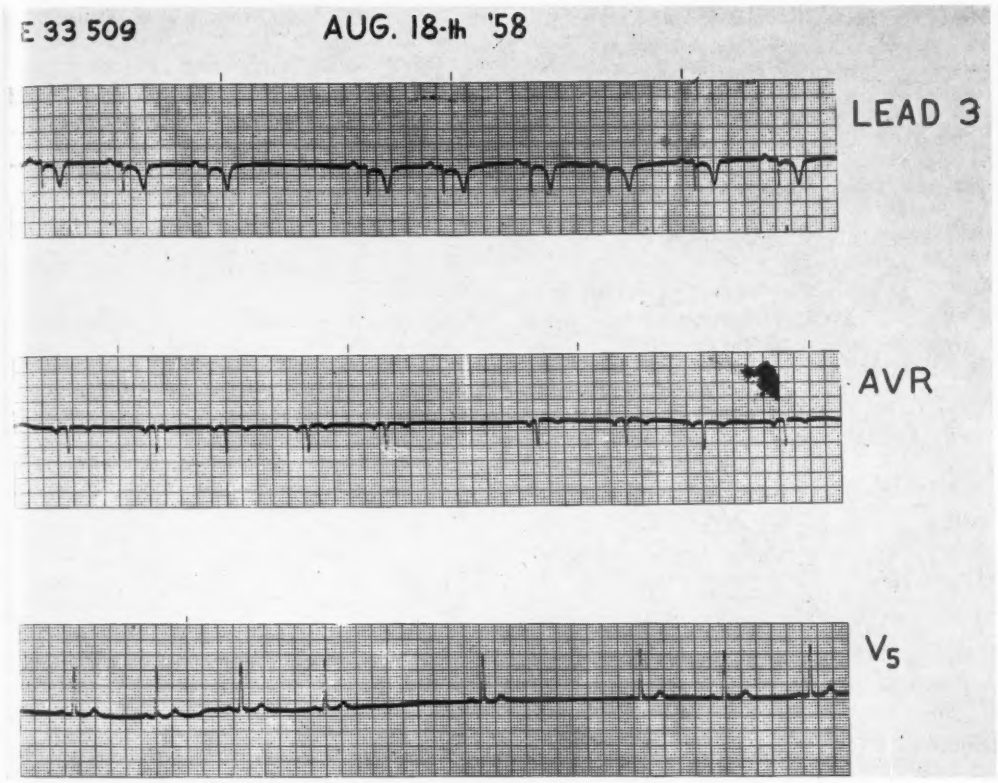

Figure 6

Electrocardiogram taken August 18, 1959, showing sinus arrhythmia, with short periods of arrest approximating 2 sinoatrial intervals.

arrest. Gold and others[10] have shown that the effect of a large dose of Digoxin, injected intravenously, on the heart rate of a patient with atrial fibrillation wears off fairly rapidly, within a period of 3 to 5 days.

When Digoxin was stopped in the second admission, shortly before vagotomy, the episodes of cardiac arrest stopped after 4 days, but he either had a well-marked sinus bradycardia, varying between 38 and 60 beats per minute, or a tachycardia similar to that seen in figure 2. Thus his rhythm was not normal and he was not comfortable.

Since vagotomy he has had no more episodes of cardiac arrest. These episodes were frequent, occurring many times on most days, during the 5 months before vagotomy. He occasionally went 3 or 4 days without being conscious of an episode of arrest in the 5-month period before vagotomy, but not longer. Tachycardia was observed very often in that 5-month period. In the time since vagotomy no further episodes of cardiac arrest have been observed, and his episodes of tachycardia have occurred 5 times, on an average of every 2 months. He is back at work, supporting his family, and is able to enjoy life. It seems that vagotomy has been followed by a worthwhile improvement in his clinical state, but no causal relation between the two can be assumed. Vagotomy is not advocated as a mode of treatment unless, as in this instance, all other therapy fails and the procedure is undertaken on an experimental basis.

Summario in Interlingua

Es presentate un caso de syncope effectuate per recurrente arrestos sino-atrial. Le episodios de arresto cardiac cessava post section del vago dextere in le collo.

Vagotomia non es recommendate como modo de tractamento excepte quando—como in le presente caso—omne altere formas de therapia se ha provate van, i.e., quando le intervention pote esser justificate como un mesura experimental.

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McCluskie, J. A. W., and Seaton, D. A.: The Value of Anticoagulant Therapy in the Treatment of Acute Myocardial Infarction. Scottish M.J. 4: 305 (June), 1959.

Two comparable groups of patients suffering first myocardial infarctions were studied from the 1952-1956 files of the Western Infirmary, Glasgow. One group of 111 patients received heparin during the first 48 hours of hospitalization and ethyl biscoumacetate or phenindione throughout hospitalization, the latter aiming to increase the 1-stage prothrombin time 2½ times above the baseline level. The control group of 115 patients received no anticoagulant and also remained in the hospital for a shorter period, averaging 25.4 days as compared with 33.9 days for the anticoagulated group. The mortality rate was 19 per cent among the treated patients and 39 per cent in the control group. Thromboembolic episodes were noted in 18 per cent of the treated group and in 34 per cent of the controls. The authors favor the routine use of anticoagulants in acute myocardial infarction.

Rogers

A Case of Kinking of the Aortic Arch

By S. Šarić, M.D., V. Vuletić, M.D., V. Gvozdanović, M.D., and B. Mark, M.D.

KINKING of the aorta is a rare anomaly in which that part of the aortic arch that passes over into the descending aorta has a double kinking in the shape of a double S. The kink lies toward the front and somewhat to the right at the level of the ligamentum arteriosum, where aortic coarctation most frequently occurs. The superposed shadow of the kinking causes an opacity on the left of the mediastinal mass parasternally. The pulsating mass "above" the aortic knuckle represents the proximal part of the kinked aortic arch, and the apparent aortic knuckle is the distal portion of the arch. There is no apparent vascular obstruction or stenosis, but there is a very marked elongation of the kinked aortic arch.

The uncommon finding of an elongated thoracic aorta was first described by Rösler and White in 1931.[1] They did not apply a new term for the malformation. The first clinical description was offered by Souders and associates in 1951.[2] Their case had been treated as Hodgkin's disease and because there was no response to x-ray therapy the patient was operated upon and the malformation of the aorta was found. They called the malformation "a subclinical form of coarctation." There followed 7 other publications[3-9] under different titles: pseudocoarctation, aneurysm of the arch, etc., yet none of these terms is appropriate owing to ambiguity. DiGuglielmo and Guttadauro[10] were the first to introduce the term "kinking of the aortic arch," which is accurate, both anatomically and clinically, in that it describes a tortuosity and a curvature in the elongated aortic arch. To date a total of about 30 cases has been described in the world literature,[11-13] 9 of these in Europe.

Most cases were free from symptoms and were first noticed on radiographic examination. In 1 of DiGuglielmo's cases it occurred in association with a ventricular septal defect.

All described cases exhibited far less tortuosity than our case, with scant clinical symptoms. A systolic murmur was heard in 2 cases above the aorta, and in 2 cases it was heard posteriorly. In only 1 case did it occur in the left intercostal region.

Another case of this unusual anomaly is reported here.

Case Report

A 21-year-old bricklayer suffered the onset of the present illness 4 months before admission to the University Hospitals, Zagreb, with the following symptoms: choking and a stabbing pain in the left chest from the left shoulderblade downward and toward the front; a sensation of a "current" in the left side of the neck and a feeling that "his head did not seem to belong to him," especially when moving it to the right; easy fatigue; rapid palpitation; and a sensation of heat all over the body. These difficulties were much increased with excitement.

He was of normal development and average body structure. Pulsation of the right carotid artery was more pronounced than the left one. The blood pressure readings were in the left arm 135/95 to 150/100, in the right arm 145/95 to 165/100, in the left leg 160/130, and in the right leg 155/120. On palpation the apex beat was prominent, with a strong impulse from the left ventricle. A slight thrill was palpated above the aorta, and the second sound could be felt. On auscultation the sounds were loud. The first sound was split, the second component being a characteristic "systolic click." The second sound above the aorta was accentuated and metallic, but the accentuated second sound disappeared 1 fingerbreadth from the sternal border. At the pulmonic area a weak systolic murmur was heard, which spread to the supraclavicular region and to the back in the interscapular area (fig. 1). No abnormal femoral or other arterial pulsation was palpated.

The electrocardiogram, circulation time, venous pressure, and oscillometric examination of arms and legs were within normal limits. The basal metabolic rate was +19 per cent.

X-ray of the lungs and heart (fig. 2) showed a semicircular opacity in the left parasternal area,

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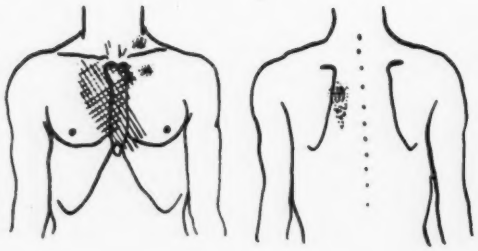

Figure 1

Auscultatory findings.

seemingly located above the aortic arch and exhibiting marked arterial pulsation. No rib erosion was noticed.

Our patient did not exhibit clinical symptoms indicating the presence of an aortic ring. The esophogram presented a pattern contrary to that observed in aortic rings, and excluded this diagnosis. Coarctation of the aorta could not be excluded completely but could not be diagnosed in the absence of any positive findings. Hence the radiologist and we reached the conclusion that we had encountered a special malformation that could not be diagnosed without angiocardiography. It disclosed a tortuosity or kinking of the aorta (figs. 3 and 4).

Discussion

In our patient the "streaming" sensation in the left side of the neck and the irradiating pain may be ascribed to the anomaly. The auscultatory findings were interpreted as follows: the systolic click indicates a vascular sound, the phenomenon is found in dilatation of the aorta or of the pulmonary artery. In calling it a click, we wish to emphasize that the sound is not associated with the closure of the mitral or tricuspid valves creating the first sound. The accentuated second sound above the aorta can be only partly explained by the hypertension, as it is heard very rarely indeed in such a mild rise of blood pressure (150/100) in a young subject. We believe that the aortic second sound was accentuated because the ascending aorta lay very close to

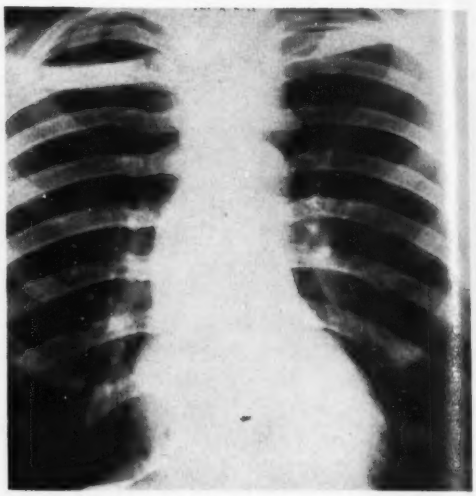

Figure 2

Anteroposterior roentgenogram. A sharply defined semispherical soft-tissue opacity is evident lying "above" the aortic knuckle, beyond the left border of the upper mediastinum.

the anterior thoracic wall because of the increased anterior curvature. In accordance with this possibility was the abrupt disappearance of this second sound exactly where the aorta curves backward, to the left of the sternum. The systolic murmur is the most difficult to explain, as, in theory, it ought not to be heard in an anomaly without either stenosis or shunt. The curvature acts hemodynamically as a sort of aneurysm, however, imposing resistance and turbulence at the sudden bends. From the embryologic aspect the anomaly develops on a similar basis as coarctation of the aorta, except that there is no stenosis.

With the exception of slight hypertension the patient usually does not experience marked disturbance. The prognosis, however, is a matter of conjecture. Pathophysiologically the anomaly appears similar to an aneurysm. Instead of the usual wide aortic arch there exist 3 curves, which sustain the full impact of the blood stream that pounds against the bends and produces an enlargement. As long as the wall remains elastic there is no impending danger of aneurysm; it becomes a menace

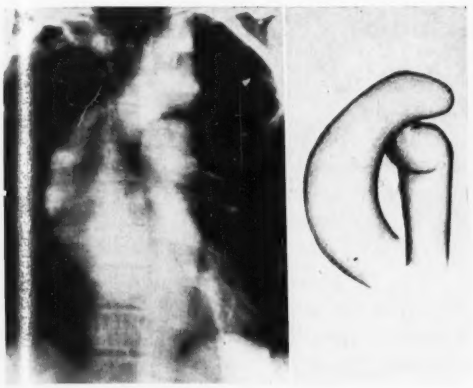

Figure 3

Anteroposterior angiocardiogram and diagram. The aortic arch is markedly elongated and exhibits a double kinking in the shape of a double S. The opacity seen in the conventional anteroposterior roentgenogram corresponds to the proximal part of the kinked aortic arch and the apparent aortic knuckle forms the distal portion of the arch.

only with the onset of atherosclerosis. The stretching of the media then creates a vicious circle. In the presence of an aneurysm the lateral pressure increases on the site of convexity and the artery widens, causing further damage to its wall. Hence aneurysms may appear in the parts most exposed to the blood stream, with possible pressure upon the surrounding organs and possibly even rupture.

The anomaly has not yet been submitted to surgery, and we do not consider it indicated in our case. The surgical risk would exceed by far the effect to be expected in cases of such slight discomfort to the patient.

Summary

A case of uncommon aortic anomaly has been described. The clinical signs as well as the differential diagnosis are stressed.

Summario in Interlingua

Es describite un caso de un incommun anormalitate aortic. Le signos clinic e le diagnose differential es presentate in detalio.

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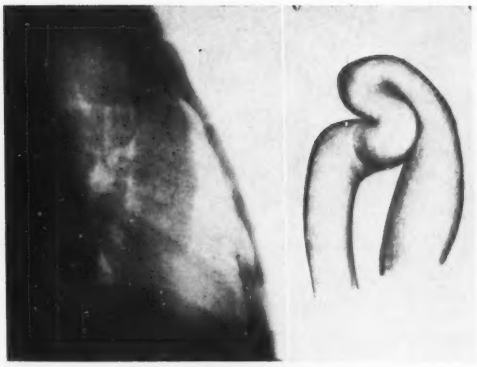

Figure 4

Lateral angiocardiogram and diagram. Distal part of kinked arch and proximal portion of descending aorta show a curvature with the convexity directed forward and downward similar to coarctation of the aorta but without any signs of stenosis.

A New Method of Left Ventricular Catheterization

By David Littmann, M.D., Oscar E. Starobin, M.D., Jack H. Hall, M.D., Robert J. Matthews, M.D., and John A. Williams, M.D.

TRANSTHORACIC and transbronchial catheterization of the left heart are presently commonplace maneuvers in the study of heart disease.[1] They are not without risk, however, and are accompanied by an impressive morbidity and a small mortality.[2-6] For this reason and because of other inherent difficulties, it has been our practice to limit these procedures to candidates for surgery, and then when the desired information not only justified the risk but could be obtained in no other way.

Recently, a considerable experience was obtained with the loop-end catheter for coronary angiography.[7, 8] This procedure is performed with a polyethylene catheter of ample proportions and special design, percutaneously introduced into the aorta by a modification of the Seldinger technic. In this manner a catheter equivalent to, or even larger than, the needle used for the puncture can be inserted into a vessel without the necessity of surgical exposure. The catheter is positioned just above the aortic valve, the contrast substance is injected, and radiographs are made. It was discovered early in this experience, and quite by chance, that the catheter could be passed into the left ventricle by advancing it several additional centimeters. The form of the catheter resulted, apparently, in such self-centering that the ventricle could be repeatedly entered without evidence of trauma to the valve cusps. Thereafter, blood samples, pressure studies, and ventriculograms could be obtained. The caliber of the catheter was such (I.D. .070 inch) that ventriculograms of fine quality were obtained following hand injection of 30 to 40 ml. of contrast substance.* Undamped pressure tracings were recorded, which were, however, somewhat deformed by turbulence resulting from the upstream position of the catheter.

Since the procedure was done with the patient in the supine position, left and right heart catheterization could be carried out concurrently. This not only saved time but permitted simultaneous registration of such phenomena as left and right ventricular pulse curves with a common zero pressure reference level and left ventricular and pulmonary wedge pressures. With conventional equipment, exercise could be performed with catheters in both ventricles. Similarly, air samples were collected and cardiac outputs were determined exactly as in uncomplicated right heart catheterization. Tracings were regularly recorded during withdrawal of the catheter from left ventricle to aorta.

Introduction of the catheter into the left ventricle was routinely performed in subsequent conventional catheterizations, and transthoracic puncture was done only when the left ventricle could not be attained in retrograde fashion.

Materials and Methods

Retrograde left ventricular catheterization was attempted in 65 patients. Two were women and the remainder were men between the ages of 33 and 68. The diagnoses included arteriosclerotic and rheumatic heart disease and a few instances of congenital cardiac deformity. A number of patients had multiple valvular lesions, and studies were performed in several in an effort to assess the relative importance of aortic stenosis and incompetence, mitral stenosis and regurgitation, and the like. Four subjects had no cardiac disorders. In patients with coronary artery disease, left heart studies were carried out in addition to coronary angiography.

All patients were premedicated with meperidine, secobarbital, and penicillin, and all were studied in the basal state, generally in the morning. Electrodes were attached and the electrocardiogram was

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*Diatrizoate methylglucamine, supplied as Cardiografin 85 per cent through the courtesy of Dr. Milton N. Donin of the Squibb Foundation for Medical Research.

monitored on a cathode-ray oscilloscope throughout the procedure.

The equipment included the usual means for obtaining local anesthesia, a small knife (no. 11 Bard-Parker) for making the skin puncture, a 3-inch short bevel, thin-wall no.-14 needle with fitted obturator, a flexible wire guide, and the preformed catheter.

The wire guide, resembling a piano string, was 115 cm. long and .060 inch thick. It was fabricated of stainless-steel wire wound around a central strand of similar material. The core was joined at one end to the outer wire by a polished silver bead but was 5 cm. shorter than the winding at the other end. This left a centerless tip, also sealed with a silver bead, which was much softer and more flexible than the remainder of the guide.*

The catheter was of polyethylene tubing with an internal diameter of .070 inch and an outside diameter of .110 inch, cut to a total length of 110 cm.† It is normally radiolucent but we have recently employed similar tubing containing metallic salts, which is visible under the fluoroscope. One end of the catheter was formed over a soft copper wire into a 2.5- to 3-cm. loop oriented at right angles to the shaft. It was then immersed in boiling water for 1 minute. After cooling, the wire was removed and the catheter retained its new form at room and body temperatures. The end was slightly constricted by stretching and 2 or 3 holes were drilled in the inferior surface of the loop.

Following local procaine anesthesia, the no.-14 needle was introduced into the femoral artery, generally the right, through a 2-mm. skin incision. When it was certain that the needle was well within the vessel, the guide was passed through it into the artery for a distance of 12 to 15 cm., soft end first. The needle was then removed over it. Bleeding around the guide normally occurred at this time and was controlled by moderate pressure. The loop end of the catheter was straightened out in the hand and threaded over the guide until it reached the skin. The wire guide was now found to extend just beyond the free end of the catheter. The catheter was then passed through the skin and subcutaneous tissues into the artery together with the wire guide. This effectively plugged the puncture site so that all bleeding stopped. The catheter and guide were advanced together for another 6 to 10 cm. The guide was then separately retracted until only the soft leading tip remained extended beyond the catheter. This position was determined before use by careful measurement of the catheter against the guide. Both were now passed together up the aorta under fluoroscopic observation. Quite frequently the guide engaged the right renal artery, less often the left. It sometimes passed into the left common carotid or the innominate artery before traversing the arch. When the end of the guide was observed at the approximate level of

Figure 1

The loop-end catheter.

*The guides were fabricated on special order and completed in our own shop. They are presently obtainable from the Codman & Shurtleff Company of Boston, Mass. Somewhat similar guides are supplied by the Schick X-ray Company of Chicago, Ill., and the Ohio Chemical Company of Madison, Wisc.

†Commercially available as PE 260 from Clay-Adams Co. of New York. When joined to a Model A (Statham) strain-gage transducer, the system has a resonant frequency of 25 c.p.s. and a damping coefficient of 1.73.

Figure 2

Normal left ventriculogram. The coronary arteries are faintly opacified.

the aortic valve, it was removed from the catheter. Eight to 10 ml. of blood were briskly withdrawn from the catheter, and a 5-per cent glucose drip containing 15 mg. of heparin was connected and regulated to maintain a flow of 30 to 40 drops a minute.* The system was connected to a strain-gage transducer and the form of the pulse curve was observed on a cathode-ray oscilloscope. When a radiolucent catheter was employed, 5 ml. of contrast substance were introduced into it and the position of the loop was checked on the fluoroscope. The catheter was slowly advanced with monitoring primarily of the electrocardiogram and pressure curves. Entrance of the catheter into the left ventricle was heralded by a characteristic drop in diastolic pressure. A few ectopic beats also appeared at this time. Passage of the loop across the aortic valve was frequently felt by the operator through the catheter and, in the presence of aortic incompetence, was likened to the sensation of a fish biting on a line. Similarly, the grating thrill of aortic stenosis was transmitted along the catheter to an extraordinary degree.

The catheter was advanced an additional 4 to 5 cm. so that it came to lie well within the ventricle. It was not manipulated further unless ectopic beats became troublesome. The whole procedure was usually accomplished within 5 minutes and fluoroscopy time, which rarely exceeded 2 minutes, might be as brief as 30 seconds. Then ventriculograms were made in some patients and pressure tracings were recorded in every instance. "Pull-through" curves were obtained as the catheter was withdrawn into the aorta and, in some patients, coronary arteriograms were made with the loop just above the sinuses of Valsalva.

In patients in whom combined studies were done, a second operator worked on the opposite side of the table and prepared the left arm while the arterial catheter was being passed. Occasionally, the venous and arterial catheters were introduced at the same time. After both catheters had been passed, resting and exercise outputs, appropriate pressure recordings, and samples were obtained. Dye curves were sometimes made and, when indicated, other maneuvers were carried out with the catheter in the left ventricle.

Results

Successful retrograde left ventricular catheterization was accomplished 53 times in 65 patients. The 12 patients in whom the maneuver failed were separately considered. In 1 subject extraordinary tortuosity of the aorta prevented passage of the catheter above the diaphragm. In 2 others the catheter proved to be too short; in one of these a second attempt was successful when a longer catheter was used. The catheter could not be maneuvered beyond the left common carotid artery in 1 patient. In 61 patients in whom the aortic valve was reached, the left ventricle was not entered in 1 in whom the loop appeared to be too small and was retained in one of the valve cusps. It seems likely, in the light of subsequent experience, that a larger loop could have been passed successfully. The valve could not be traversed in 7 others who had aortic stenosis. When the catheter was advanced too far, it buckled, doubled back on itself, or coiled. Partial ventricular penetration was effected in 3 subjects with apparent aortic stenosis. One of these patients had been studied by transthoracic catheterization at a previous date and showed no gradient across the aortic valve. The more recent studies confirmed this finding. Although ventricular pressures could be re-

*The no.-14 thin-wall needle employed in the arterial puncture fits snugly into the catheter and serves as a connector between it and the other apparatus.

corded, interference with free progress of the catheter through the valve suggested deformity. Passage of the catheter into the left ventricle occurred with ease in all other patients. It traversed the mitral valve in 1 patient without mitral disease.

Representative pressure determinations and ventriculograms are illustrated in figures 1 to 5.

There was no cardiac morbidity resulting from the procedure in the 61 patients in whom the aortic valve was reached or traversed. In no instance was there any evidence of injury to the cusps. Injection of the contrast substance was followed by the characteristic flush, rarely by vomiting, and by rather slight and transient electrocardiographic changes in a few. More striking abnormalities have been noted during coronary angiography.[8] Ventricular ectopic beats, which appeared upon introduction of the catheter into the left ventricle, generally cleared spontaneously. In a few, not over 10 per cent, repositioning of the catheter was required. In no instance did disturbance of rhythm occur to a degree that necessitated termination of the procedure.

Introduction of a large needle into the femoral artery was one of the more difficult steps in the procedure. Considerable practice with smaller needles was required in order that the puncture could be performed quickly and without injury to the artery or surrounding structures. Passage of the wire guide through the needle constituted a potential hazard. Despite the softness of the flexible tip, injudicious forcing has resulted in perforation of the aorta and in retroperitoneal bleeding. This led to a hematoma of extensive proportions in one of our first patients. After close observation for several hours, surgical exploration was performed and the hematoma was evacuated. Bleeding, which had stopped, had occurred through a perforation at an arteriosclerotic plaque. This patient had received over 50 mg. of heparin in the arterial drip and this was thought to have contributed to the persistence and extent of the hemorrhage. Similar mishaps of lesser proportions not requiring surgical relief occurred twice early in our experience. In all more recent cases, however, free, uninhibited, and painless passage of the guide has made for complete freedom from injury. Though firm pressure is maintained over the puncture site in all patients, large ecchymotic areas occur about half the time. Knotting of the catheter occurred once with an overlong loop. This took place at the puncture site. Removal was effected after surgical exposure of the femoral artery. Prompt and uncomplicated recovery followed.

Figure 3

Left ventriculogram in a patient with mitral regurgitation.

Discussion

Needle puncture of the left atrium or ventricle is a potentially hazardous procedure that, even in the best hands, carries with it a definite morbidity. There is a natural inclination to hurry the operation in order to lessen the possibility of cardiac laceration and tamponade. The catheters that can be passed through the needle are quite small and subject to obstruction, angulation, knotting, and even shearing. The pressure curves obtained through them are frequently damped and sometimes unreliable. The advantages inherent

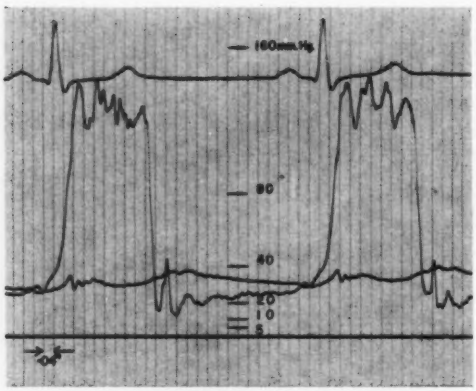

Figure 4

Top, *electrocardiogram;* middle, *pulse wave recording in left ventricle;* bottom, *pulmonary wedge position.*

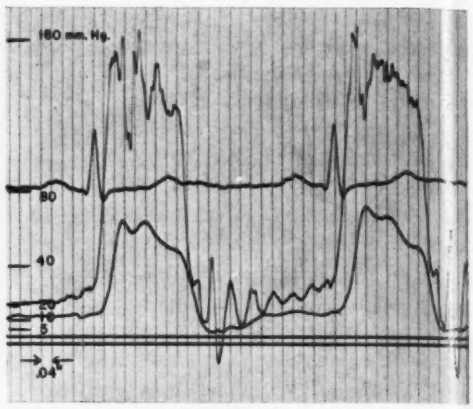

Figure 5

Pulse wave recording. Electrocardiogram, left ventricle, right ventricle.

in the large, relatively stiff-walled catheter used in the retrograde method are self-evident. Additionally, the almost complete lack of trauma and the rapidity with which the catheter can be introduced into the left ventricle make for an unhurried and thorough examination. The loop catheter has been allowed to remain in the left ventricle for over an hour without difficulty. Ventricular irritability has not been a problem. Passage of the catheter across the valve causes no discomfort or sensation. The cusps are apparently protected from injury by the perpendicular orientation of the tip to the long axis of the aorta. Accordingly, the flat of the catheter and not the potentially traumatic tip presents at the valve. The junction between shaft and loop is, apparently, the first part of the catheter to enter the ventricle. The loop follows. Not enough disturbance of valve function takes place to produce an audible murmur.

Excluding instances with obvious technical difficulties, passage of the loop catheter into the left ventricle is so regularly accomplished that failure to advance beyond the valve is presently considered to be due to important valvular deformity, generally aortic stenosis. On 3 occasions the aortic valve was partially traversed in patients with murmurs of aortic stenosis who did not, however, have interference with function.

No attempt is made in this report to stress the usefulness of left ventriculography, and none seems necessary. The simplicity and safety with which this maneuver is performed through the retrograde catheter is such, however, that it may well prove to be the most direct and useful means for the determination of mitral insufficiency and ventricular septal defects. Criteria for the estimation of the degree of mitral incompetence by left ventriculography have already been proposed,[10] and further experience will doubtless add to the precision of such determinations.

Excellent studies of electromechanical events are possible, particularly those related to bundle-branch block. Coincident right and left ventricular pressure curves are recorded together with the electrocardiogram. The ease with which such studies can be obtained has stimulated a renewed interest in such problems.

Simultaneous recordings of left ventricular curves and pulmonary wedge pressures have been made and are entirely satisfactory for the estimation of mitral valve gradient. Although the catheter entered the left atrium in one patient without mitral disease, it appears unlikely that the loop could have been directed through a stenotic valve or, with any regularity, through the normal mitral valve.

The unhurried and nonirritating presence

of a large catheter in the left ventricle has also permitted the registration of dye-dilution curves in both directions and the collection of blood samples for the determination of shunts.

Summary

A description is presented of a rapid and relatively uncomplicated method of left heart catheterization. It is possible in this manner to obtain many types of left ventricular studies and ventriculograms of diagnostic quality. A special loop-end catheter is employed, which is percutaneously introduced into the aorta and which regularly enters the left ventricle through the aortic valve except when this valve is stenosed or deformed. This entry is accomplished without apparent injury to the heart.

Summario in Interlingua

Es describite un rapide e relativemente pauco complexe methodo de catheterismo sinistro-cardiac. Le methodo permitte le effectuation de multe studios sinistro-ventricular, incluse le obtention de ventriculogrammas de qualitate diagnostic. Es usate un catheter special a termino ansate que es introducite percutaneemente in le aorta e que entra regularmente in le ventriculo sinistre via le valvula aortic, excepte in casos de stenosis o malformation del valvula. Le entrata es effecutate sin apparente damno al corde.

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Jenab, M., Lade, R. I., Chiga, M., and Diehl, A. M.: Cardiorespiratory Syndrome of Obesity in a Child. Case Report and Necropsy Finding. Pediatrics 24: 23 (July), 1959.

A case of the "Pickwickian syndrome" is reported which occurred in a 6-year-old child and is believed by the authors to be the first reported case of this syndrome in children. This child presented the clinical features of the cardiorespiratory syndrome of obesity with associated polycythemia, cyanosis, dyspnea, somnolence, congestive heart failure, and, in addition, mental retardation. No definite evidence of pulmonary disease was found at necropsy.

Karpman

Severe Congenital Pulmonic Stenosis without Marked Right Ventricular Hypertension

By JOHN M. VEROSKY, M.D., AND E. S. CROSSETT, M.D.

IN THE literature, indications given for surgical correction of congenital pulmonic stenosis have emphasized chiefly the degree of right ventricular hypertension or the gradient across the obstructed orifice.[1-4] We wish to present 2 cases of severe stenosis, as judged by the size of orifice visualized at operation, in which right ventricular systolic pressure was less than 90 mm. of mercury. Both these children had decreased cardiac output and severely retarded growth. In contrast, 2 patients with equally severe stenosis are presented who had marked hypertension.

Method

All patients had investigations consisting of history, physical examination, radiographic studies of the chest, electrocardiography, and right heart catheterization. In each case the clinical findings were typical of pulmonic stenosis and will not be reiterated here. In all, pulmonic stenosis was present as the sole cardiac malformation. In one, (L.S.), a small right-to-left shunt through a patent foramen ovale was present. Catherization was performed under local anesthesia and sedation (25 mg. meperidine, 6.25 mg. chlorpromazine, and 6.25 mg. promethazine). Electrode catheters were used as an aid in locating the catheter tip. Pressures were measured by a calibrated Statham P23AA electromanometer. Oxygen content was determined with a standardized Waters cuvette. Data were recorded with an oscilloscopic photographic recorder (Electronics for Medicine Model PR 6).

In L.S. and K.E. cardiac output was determined by use of the Fick principle. The Gorlin formula[5] was then used to calculate valve size. Systolic ejection period (S.e.p.) was timed from the pulmonary artery pressure tracing, measuring from the beginning of the systolic rise to the dicrotic notch. Right ventricular systolic mean pressure (RV_{sm}) was determined planigraphically from the right ventricular pressure tracing during systolic ejection.

All patients were operated upon under direct vision, by means of extracorporeal circulation; for P.M., a bubbler oxygenator was used; for the others, a multiple rotating disk oxygenator was used. Size of the pulmonary orifice was determined visually by the surgeon at the time of operation.

The data of Paul and Rudolph[6] were used as a basis for normal pulmonary valve sizes. Because of the limited number of cases of any given age listed in their study, these figures can be taken as approximations only.

Weight and height were evaluated by the standards of Howard V. Meredith, Iowa Child Welfare Research Station, and the Harvard School of Public Health Studies of Child Health and Development;[7] some extrapolation from these tables was necessary to evaluate L. S. Surface area was determined from the nomogram derived by R. R. Hannon from the formula of Dubois and Dubois.[7]

Postoperatively, the right ventricular index was calculated from catheterization data previously obtained, but the size of the pulmonary orifice observed was used in the equation,

$$\textit{Right ventricular index}\ (\text{L./min./M.}^2) = C\sqrt{\frac{g}{\frac{\pi}{4}D^2}}\sqrt{\frac{RV_{sm}-PA_{sm}}{S.\ A.\ (1000)}}\ \Sigma\ S.\ e.\ p.$$

in which C is a constant, taken as unity, g is the acceleration due to gravity, Σ *S. e. p.* is the sum of systolic ejection periods (sec./min.) and *S. A.* is the surface area in $M.^2$

Results

Data are listed in table 1. The lack of correlation between symptoms, heart size, and severity of stenosis is well known and was not surprising. These cases, however, show a more disturbing lack of correlation between the degree of right ventricular hypertrophy electrocardiographically, right ventricular pressure, and severity of stenosis, if these factors are considered without regard to cardiac output and growth pattern.

Discussion

For an opening of given size, the Poiseuille equation (resistance equals pressure gradient divided by flow) demands that the pressure

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Table 1

Four Cases of Congenital Pulmonic Stenosis

Patient	K. E.	K. C.	P. M.	L. S.
Age, years	5 5/12	4 9/12	7 5/12	19 3/12
Weight, pounds	33	33	49	164
percentile	3rd	3rd	10th	75th
Height, inches	43	39	48	72
percentile	25th	3rd	25th	90th
Surface area, M.^{2}	0.67	0.63	0.87	1.95
per cent of normal age	77	87	92	111
Type of stenosis	infundib.	valvular	valvular	valvular
Symptoms	mild	mild	moderate	severe
X-ray cardiothoracic ratio	0.53		0.59	0.58
R wave (mm.) in V_1 or V_{3R}	16	25	25	22
Catheter size	6E	6E	7E	8E
Right ventricular index, L./min./M.^{2}	1.55	—	—	0.72
Right ventricular pressure, mm. Hg*	74/10 (43)	84/10 (59)	196/4 (70)	145/10 (47)
Pulmonary artery pressure, mm. Hg*	12/7 (9)	16/11 (14)	6/3 (4)	10/3 (5)
RV_{sm} - PA_{sm} mm. Hg	28	22	80	46
Σ S.e.p., sec./min.	36.6	44.1	32.4	23.5
S.e.p., sec./beat	0.30	0.45	0.36	0.36
Pulmonary orifice area, cm.^{2} calculated	0.12	—	—	0.2
Observed during surgery	0.16	0.20	0.13	0.28
Normal for age	1.9	1.8	2	4
Pulmonary orifice diameter, mm. calculated	4.0	—	—	5.0
Observed during surgery	4.5	5	4	6
Normal for age	15.6	15.2	16	22.6
Right ventricular index, calculated from valve size observed during surgery L./min./M.^{2}	2.06	1.61	1.93	1.04
Right ventricular index, calculated from valve size observed during surgery, assuming normal weight and height, L./min./M.^{2}	1.59	1.41	1.77	1.15

*Mean pressure in parentheses.

will fall as flow decreases. In the Gorlin formula,

$$Area = \frac{Flow}{constant \times \sqrt{pressure\ gradient}}$$

the same relation is seen. It is thus not proper to term a stenosis as mild if the pressure is only mildly elevated because of reduction in flow. It would seem more reasonable to call a very small pulmonic opening a severe stenosis, since mathematically this will cause either severe right ventricular hypertension and strain or reduced cardiac output; in some children, the latter may prevent normal growth.

The natural history of pulmonic stenosis is still incompletely known. It has not been determined if the size of the orifice remains constant or changes with age. If it does not enlarge with age, it is clear that right ventricular pressure must increase if the cardiac output is to increase as growth requires. Until more information is available of the course of

these events, it would seem that the single most important measure of severity is the size of the opening itself.

Some cautious speculations can be made on the course of the patients presented. In P. M. the stenosis was so severe that increase in cardiac output to accompany completely normal growth was not possible. At the same time, a fair output for his moderately stunted size was maintained, at the cost of severe right ventricular hypertension, as reflected in the electrocardiogram. In L. S., the same factors were operative, except that cardiac output increased to allow good growth; then cardiac output decreased. It is very likely that progressive deterioration occurred over the recent years, since cyanosis at rest had been noted by the parents for only about 1 year. In K. E. the stenosis was so severe that neither normal growth nor normal cardiac output for her small body size could be achieved. Severe right ventricular hypertension was absent, and the R in V_1 was only moderately high. Yet, in view of her lowered cardiac output and calculated small orifice size, we rated her as severe. Apparently the R wave in V_1 can be taken as a measure of severity of the stenosis only if marked right ventricular hypertrophy had been present. In K. C. the R was very high and the stenosis severe, yet the hypertension was only moderate. It may be that once his right ventricular pressure was much higher than that observed at catheterization, and subsequently fell with reduction in cardiac output; it is probable that his stenosis has always been sufficiently severe as to prevent the increase in cardiac output necessary for normal growth and development.

Thus, various courses are possible in any one patient. We have no proof that the retarded growth observed was a result of reduced cardiac output, but this conclusion seems quite likely. All 4 patients grew in socioeconomic situations favorable to normal growth. We have no idea why some children with severe pulmonic stenosis respond mainly in the direction of retarded growth while others respond mainly with increasing right ventricular hypertension.

To emphasize the importance of evaluating the growth of the child, we have added to table 1 the results of recomputing the right ventricular index that our patients would have had if their cardiac outputs had been the same at body sizes normal for their ages. All patients had orifices approximately the same in size, and these normalized right ventricular indices are all much the same.

Before deciding to delay catheterization, one must evaluate the factors concerned: (1) symptoms, the least reliable measure, (2) heart size, similarly of limited value, since the reliability of the radiograph to determine concentric hypertrophy is low, (3) electrocardiogram, usually but not always completely reliable, since it is dependent upon right ventricular hypertrophy, and (4) growth and development. If serious abnormality is present in any of these, catheterization should be done.

Before deciding that stenosis is mild enough to delay operation, one should obtain an evaluation of the valve size, using as exact methods as possible, at the same time recognizing the influence of approximation factors and the sources of error involved in the clinical application of Gorlin's formula. It has been widely appreciated that severe stenosis with deterioration and congestive failure, as seen in an occasional young infant, can result in only moderate right ventricular pressure readings; this situation is not likely to mislead the clinician, because the severity of the acute symptoms calls for immediate operation. Several authors[1, 3, 8] have noted that pressure should not be the sole criterion, but there are few explicit additional criteria. At this time we could not recommend that all cases of pulmonic stenosis be repaired, and cannot accept Zimmerman's criterion for operation (a gradient of 20 mm. or more across the valve).[3] At the same time, we believe that it is possible to delay operation unwisely in the occasional child in whom only moderate electrocardiographic and manometric abnormalities are present, if the relations outlined above are ignored. From the reports of others, it is apparent that severe physical underdevelopment is not common in congenital pulmonic steno-

sis; Zimmerman and co-workers[3] mentioned that underdevelopment may occur; Kjellberg et al.[9] reported 32 cases of pulmonic stenosis, none of whom had physical dimensions below 2 standard deviations of the mean.

We are unable to correlate prognosis with definite valve sizes, but rough calculations show that it is impossible to maintain a cardiac output of over 3 liters per minute per square meter and a normal rate of growth with right ventricular hypertension below 90 mm. of mercury if the valve is less than one half the normal diameter or one fourth the normal area for age. However, our cases had valves much smaller than these conservative tolerances. It is unlikely, in our opinion, if actual calculations are carried out, that many equivocal cases will be found.

Acknowledgement

We are indebted to our anesthetist Dr. Jack Walker, and Dr. Jesse A. Hancock, Ph.D. in chemistry, for their assistance throughout various phases of this study.

Summary

Obligatory relations exist between orifice size, flow, and pressure gradient across a stenotic pulmonary valve. If the cardiac output is reduced, the patient may have severe stenosis and present only moderate right ventricular hypertension. This situation may be an acute one, which will produce progressive symptomatology, or a chronic one, which, in the growing child, will produce poor physical growth. Catheterization should be done if any of the following is present: severe symptoms, severe right ventricular hypertrophy electrocardiographically, or evidence of reduced cardiac output (such as otherwise unexplainable poor physical growth). Operation is urgently indicated if catheterization reveals either right ventricular systolic hypertension greater than 90 to 100 mm. of mercury or if there is evidence of a very small pulmonary orifice.

Summario in Interlingua

Relationes de character obligatori existe in casos de stenosis del valvula pulmonar inter le dimensiones del orificio, le fluxo, e le gradiente de tension ab un latere del sito stenotisate. Si le rendimento cardiac es reducite, il es possible que le patiente ha grados sever de stenosis sed presenta solmente un moderate hypertension dextero-ventricular. Iste situation pote esser acute, producente un symptomatologia progressive, sed illo etiam pote esser chronic, producente—in juveniles in crescentia—progresso crescential non satisfactori. Catheterismo es indicate in le presentia de ulle del sequente constatationes: Symptomas sever, signos electrocardiographic de sever hypertrophia dextero-ventricular, o evidentia de un reducite rendimento cardiac (como per exemplo alteremente inexplicabile inadequatia del crescentia physic). Intervention chirurgic es indicate urgentemente si le catheterismo revela hypertension systolic dextero-ventricular in excesso de 90 a 100 mm de Hg o si il ha provas de un micrissime orificio pulmonar.

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The Electrocardiogram in Population Studies

A Classification System

By Henry Blackburn, M.D., Ancel Keys, Ph.D., Ernst Simonson, M.D., Pentti Rautaharju, M.D., and Sven Punsar, M.D.

EPIDEMIOLOGIC studies on coronary heart disease are only in their beginnings but they have already yielded important clues and hypotheses regarding development, prognosis, etiology, and possible methods of prevention.[1-7] It is now certain that there are important differences in the frequency, at a given age, of severe atherosclerosis, myocardial infarction, and death from coronary heart disease, among populations and among social and activity classes in given populations, and even in the same populations at different times.[8-20] These differences appear to be related to differences in the mode of life, i.e., they clearly suggest the possibility that such investigations may reveal principles on which preventive programs may be based.

But the data now available are seriously deficient in regard to the actual prevalence and incidence of coronary heart disease in all populations, not only because of defects in vital statistics but also because of questions in survey data. In surveys there are often inadequacies of sampling but at least equally important are uncertainties in the diagnosis. The diagnosis of coronary heart disease is made most securely on the basis of autopsy material but autopsies almost never represent valid samples of the dead, let alone of the living, population and there is as yet no agreement among pathologists about quantitative grading of the arterial and myocardial lesions. In any case, autopsies with adequate reports on the heart are uncommon in many countries, and even the best autopsy data on coronary heart disease primarily reflect disease processes begun years ago and therefore have limited value in evaluating present and future tendencies.

It is necessary, then, to consider the diagnosis of coronary heart disease in living members of the population. Acute myocardial infarction can be diagnosed with a high degree of reliability on the basis of the clinical picture and serial electrocardiograms, aided by hematologic data and serum enzyme levels. In population studies, however, the main problem is in the recognition of chronic coronary heart disease and here very difficult questions arise. Coronary *artery* disease in itself, without any manifestation of myocardial involvement, is the submerged portion of the iceberg and remains largely invisible.

The diagnosis of angina pectoris may be made with considerable security in typical cases by skilled cardiologists. But there are many atypical cases, and at best it is difficult to provide objective documentation of the diagnosis. Chief reliance in the *objective* diagnosis of coronary heart disease is placed on the electrocardiogram, and it is clear that all surveys of populations in regard to coronary heart disease must lean heavily on the electrocardiogram. In this area, electrocardiography is a crucial tool.

Unfortunately, the electrocardiogram is specifically pathognomonic in only a few situations. Most deviations from normality are nonspecific and there is no general agreement among clinicians and electrocardiographers about (pathologic) diagnostic interpretation of the majority of electrocardiographic deviations or about their implications for present cardiac status or prognostic cri-

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Aided by research grants from the American Heart Association, New York, the U. S. Public Health Service (H-10, recommended by the Cardiovascular Study Section of the National Heart Institute), and the Winton Companies Fund, Minneapolis, Minn.

teria even for old myocardial infarction are by no means standardized. Moreover, the difference between clinical practice and epidemiologic studies with general populations must be noted. An electrocardiographic deviation which appears to be highly correlated with a specific pathologic situation observed clinically or at autopsy in a hospital population of sick or recently dead patients may be poorly correlated with manifest disease in a working population or one screened for clinical "health."

In view of these facts, much uncertainty exists about the actual electrocardiographic findings when, as in most population surveys, only descriptive clinical terms of "infarction," "angina pectoris," and "coronary" or "arteriosclerotic" heart disease are used. As regards electrocardiographic diagnosis per se of coronary heart disease, there are wide differences in interpretation among experts reading independently. In a study in Wales of records from 132 men, the 3 expert electrocardiographers agreed that "ischemic heart disease" was indicated in 22 records, 2 of the 3 agreed on 8 more cases, and one or another of the 3 gave this interpretation to 26 additional records.[21] Accordingly, there is serious question of the comparability of the data on the prevalence and incidence of coronary heart disease as reported in substantially all epidemiologic studies to date.

In an attempt to secure at least internal consistency in the epidemiologic studies conducted by this laboratory, we have developed a classification scheme that we have found suitable in application to population surveys and subsequent statistical analysis. In the hope of arriving at a system with wide acceptability, we have polled many leading cardiologists in the United States and in 10 other countries and have had conferences with many experts in the U.S.A. and abroad.

From this experience it is clear that only a few electrocardiographic patterns will be accepted as specifically indicating coronary heart disease. For many "abnormal" electrocardiograms it is impossible to approach unanimity of opinion on diagnostic labeling. This is true not only for the all-or-none classification of "coronary heart disease" or "no evidence of coronary heart disease," but applies to probabilistic labeling in terms of "definite," "probable," or "possible." Agreement is almost as bad on the diagnostic electrocardiographic labels of "normal," "abnormal," or "borderline."

This does not mean that electrocardiographers disagree greatly about what items to look for or how to measure them nor that an agreed objective classification, devoid of interpretation, is impossible. Accordingly, we have attempted to provide, in the words of the recommendation of the Research and Social Committees of the International Society of Cardiology, "reporting of findings in uniform, clearly defined, and objective terms with the least risk of confusion in regard to interpretation. Emphasis should be placed on reporting the actual findings without recourse to interpretation which would follow later."[22]

A preliminary version of the system was presented at Brussels and was noted in the Joint Report (ibid., above). "Without endorsing the details of this system, it is agreed that some such system, after further testing and modification, may be recommended for application in wider research, not to supplant the usual clinical interpretation but simply to provide an agreed framework suitable to statistical analysis without prejudice to any interpretation." A subsequent revision was considered by the Committee on Criteria for Diagnosis of Heart Disease and Clinical Evaluation of the Princeton Conference on Methodology (April 1959, sponsored by the American Heart Association and the National Heart Institute of the U.S. Public Heart Service) which reported, "These criteria embody a concept strongly endorsed by the Committee, viz., electrocardiographic interpretation is, properly, an objective description of bioelectrical phenomena; the diagnostic interpretation of the electrocardiogram should be made only after collation of all clinical data."

The resulting classification system presented here is adapted to the usual reading technics

Table 1

Inter-observer Reliability. (One Hundred Thirty-two Mixed Resting Records. Independent Readings by Three Observers.)

Item	Code no.	No. observers agreeing 1	2	3	Total no. tracings
Nothing reportable	I, 0	5	10	63	78
Q and QS items	I, 1-3	3	4	20	27
Axis items	II, 1, 2	1	1	6	8
High R waves	III, 1, 2	1	2	3	6
S-T depression	IV, 1-3	6	2	14	22
T-wave items	V, 1-3	2	4	31	37
A-V conduction	VI, 1-4	4	2	0	6
Ventricular conduction	VII, 1-4	0	2	6	8
Arrhythmias	VIII, 2-6	0	0	0	0

Table 2

Intra-observer Reliability. (Resting and Post-exercise Electrocardiograms in 300 Consecutive Railroad Survey Subjects Repeated Readings Three Months Apart by One Observer.)

Item	Code no.	Reported Twice	Reported Once
Nothing reportable	I, 0	195	21
Q and QS items	I, 1-3	15	1
Axis items	II, 1, 2	3	1
High R waves	III, 1, 2	10	0
S-T depression	IV, 1-3	8	4
T-wave items	V, 1-3	8	5
A-V conduction	VI, 1-4	4	1
Ventricular conduction	VII, 1-4	6	0
S-T postexercise	XI, 1-5	33	4
T-postexercise	XII, 1-5	6	7

of the electrocardiographer. Though the first impression may be that of a maze of detail, it has been found on application by a number of electrocardiographers to be practicable. The electrocardiographer makes an inspection of the tracing at his accustomed speed. The experienced reader quickly estimates items of rate, rhythm, and axis, and detects deviations in interval, amplitude, and configuration, and he readily finds within the system the numerical code for the item he wishes to report. The organization and numbers soon become familiar. Attempts at gross simplification of the system have been found in practical trials effectively to reduce rather than to enhance its accuracy and applicability. There is provision for other items of interest only to the individual reader, and certain items may be specified as not sought for or as not tabulated by the individual reader. The requirements of modern data processing with punch-card machines have been kept in mind, and a code for this purpose is provided.

Application of the System

Reliability

Reproducibility of results in independent readings has been determined in several applications. Records were scanned at an average speed of 60 subjects per hour for before and after exercise tracings in studies of working populations, and at a somewhat slower speed in test records that had a higher proportion of abnormal cases. Table 1 presents results of inter-observer variability in 132 mixed records read independently by 3 readers. One hundred of these records referred to consecutive alphabetic names in a British field study, furnished by Dr. Ian Higgins of Llandough Hospital, Cardiff, and 32 were the records of the "coronary" cases from the Framingham Heart Study, furnished by Dr. Thomas Dawber. The over-all agreement is by no means perfect, but is, we believe, a satisfactory result of the single rapid readings, particularly for the items of greatest interest (Q and QS, ST, and T). A second round of independent readings by each observer significantly improved the agreement. Those disagreed upon were essentially in a questionable category due to beat-to-beat variability in measurements, or were simply missed, or were due to technical imperfections or inadequacies in the tracings.

Table 2 presents results of a single rapid reading by one observer on 2 occasions 3 months apart. These were records before and after exercise of 300 men, aged 40 to 60, examined consecutively in a railway population study under the direction of Dr. Henry L. Taylor of this laboratory. Again, in view of the scanning technic, agreement is not bad for the 2 most significant items, Q and QS and S-T depression after exercise. Observing the hard fact of unreliability of repeat clinical

measurements is a humbling experience, and one highly recommended.

In addition to the technical difficulties in measuring intervals and amplitudes and the rapid reading, which explain most of the disagreement between observations, some further explanation for the intra-observer variability may be worthwhile. In table 2 the disagreement on item I, 0, no reportable finding, is quite understandable, and does not mean that a record has been interpreted as "normal" on one occasion and "abnormal" on another. Usually such items as RR′ waves in V_1 or qualitative P or T wave changes are detected on one scanning and not on the other. Q and QS items on occasion shift between code I 1, 2, 3 and the technically questionable category, or to a qualitative QRS finding (codes IX 8 or 3), but will almost invariably be coded somewhere for reference in follow-up studies. The observer involved in readings for table 2 is inconsistent in recording the lesser S-T and T-wave items when a Q and QS item has been reported, and often does not record an S-T or T-wave item when one or the other is present. These omissions do not greatly affect any final compendium of diagnoses, but they are a source of consistent error by that reader.

In the Welsh study of Thomas, Cochrane, and Higgins,[21] final tabulations were based on an "electrocardiographic index," that being the number of cases in which all 3 observers agreed upon the diagnosis of "ischemic heart disease." We heartily concur in the desirability of independent observations, and routinely employ readings by 2 observers experienced in the application of this system. This is probably the most reliable, and in the long run, most efficient practice when large numbers of records must be processed. In the final analysis it would be completely objective to report, for example, all cases in which the 2 observers agree upon electrocardiographic item Q and QS I, 1. Differences in diagnostic *interpretation* are not involved with this system, however, and the differences in items tabulated are due to those that are simply missed or to beat-to-beat variations in intervals and amplitudes. Under these circumstances a subsequent review, by the observers met together, of all records in which independently assigned codes disagree, considerably enhances the applicability of the system.

Table 3

Classification of the Resting Electrocardiogram Screened "Normal" Railroad Employees

Item	Code no.	No. men	Per cent of men
Nothing reportable	I, 0	383	82.7
Q and QS items	I, 1-3	6	1.3
Axis items	II, 1, 2	15	3.2
High R waves	III, 1, 2	8	1.7
S-T depression	IV, 1-3	2	0.4
T-wave items	V, 1-3	8	1.7
A-V conduction	VI, 1-4	0	0.0
Ventricular conduction	VII, 1-4	3	0.6
Arrhythmias	VIII, 2-6	8	1.7

Findings in "Known" Populations

The validity of the electrocardiogram as a test of coronary heart disease is not established quantitatively, though an earlier attempt in this direction has been made.[23] Actually, an important by-product of epidemiologic studies, particularly those of longitudinal design, is information on the validity of certain diagnostic indices. The criteria used in this classification system obviously come from such heterogeneous sources of information[23-35] that no quantitative estimate of their validity can be made. Thus, it was of interest to apply the criteria and classification in "known" groups of clearly defined normality or pathology. Six hundred consecutive subjects of the railroad-employee study previously mentioned, ages 40 to 60, were carefully screened by many clinical criteria except electrocardiographic. Those were eliminated with medical history, physical findings, or laboratory evidence of the following: peptic ulcer, unoperated gallbladder disease, thyroid disease, diabetes, renal disease, rheumatic fever, any clinical cardiac diagnosis, chronic bronchopulmonary disease, murmurs over grade II, and blood pressure of 160 systolic or 95 diastolic or more.

Table 3 gives the distribution of electrocardiographic items in the well-screened, resid-

Table 4

Classification of the Electrocardiogram in 100 Cases of Old Anterior Myocardial Infarction "Proved" by Subsequent Autopsy and Other Means

Item	Code no.	Per cent of men
Nothing reportable	I, 0	2
Q and QS items	I, 1-3	91
Axis items	II, 1, 2	12
High R waves	III, 1, 2	1
S-T depression	IV, 1-3	26
T-wave items	V, 1-3	91
A-V conduction	VI, 1-4	1
Ventricular conduction	VII, 1-4	10
Arrhythmias	VIII, 2-6	9

ual "normal" sample of 463 men. Almost 83 per cent had no reportable electrocardiographic item and slightly over 1 per cent had Q waves of sufficient amplitude or duration to be included. Only 1 case met the criteria for class I, 1, Q and QS items; this was due to a Q wave of 0.05 second in lead III.

Table 4 presents results of applying the classification system to a well-defined "abnormal" population. From over 1,000 hospital charts bearing the clinical diagnosis of myocardial infarction, 100 cases were selected according to one of the following criteria:

1. A follow-up electrocardiogram was available, which was taken not less than 3 months after infarction and a prior acute anterior infarction was well documented by clinical history and serial electrocardiograms during the acute phase, showing typical QRS, S-T segment, and T-wave evolution among leads I, II, aV_L, V_1–V_6.

2. An electrocardiogram was available for cases dying in hospital with necropsy findings of healed infarction or well-described extensive fibrosis of the septum, anterior, apical, or lateral left ventricular wall.

Thus, late follow-up records were used for analysis from cases of anterior infarct established by clinical criteria or necropsy. Ninety-one per cent of this group had Q or QS criteria reportable under the classification system, and 2 per cent had no reportable electrocardiographic item. (It is well known that Q or QS waves may never appear or may disappear after infarction and it may be quite impossible to differentiate such cases from normal.) The degree of overlapping between this well-defined normal and abnormal group of anterior infarct cases is thus quite small. This is to be expected in highly preselected material. There is evidence that application of comparable criteria will not discriminate normal cases from cases of old posterior infarction.[23]

Diagnostic Validity

Diagnosis is, in the end, an expression of a degree of probability. It is possible that a systematic approach to clinical and electrocardiographic data will eventually permit expression of this probability as a quantity. Obviously, many of the classification criteria in this system are arbitrary, and much information is still needed from electrocardiographic-clinical-pathologic correlations and from longitudinal epidemiologic studies. Since no good estimate of the validity of the criteria is available from their source, it is of interest to apply the data from distribution of items in the "normal" and "abnormal" groups of tables 3 and 4, in which it is found that Q and QS items of the classification are a highly discriminative index. Q and QS items are used simply as an example, to obtain an impression of the ability of the classification to discriminate "normal" from "abnormal." Further consideration is made of the "specificity" of these Q and QS items for "coronary" or "arteriosclerotic" heart disease, though these questions are only indirectly involved in the actual application of the system.

For this example, let us take the data from tables 3 and 4 at their face value and assume that the distribution of Q and QS items (1.3 per cent) in the railroad group (table 3) represents actual "false positive" diagnoses in normal persons, and the Q and QS items (91 per cent) or their absence (9 per cent) in the anterior infarct group (table 4) represents in reality correct and missed diagnoses of old anterior infarction. For all Q and QS items combined (code I, 1, 2, and

3) we assume in application 1.3 per cent false-positive diagnoses in normal subjects, 9 per cent missed infarcts, and 91 per cent correct infarct diagnoses.

These 2 distributions from normal and infarct groups are employed in table 5 to determine the numbers of false-positive, missed, and correct diagnoses in 2 *hypothetical* populations. One is a proposed general population made up of 990 normal men and 10 men with old anterior infarction (group A), the other a hospital population of 900 men without infarction and 100 with old anterior infarction (group B).

An error ratio is expressed as the total number of diagnostic errors (false abnormal and missed "infarcts") divided by the number of correctly diagnosed "infarcts."

In the general or random population (A) approximately 22 cases (12.9 plus 9.1) per thousand will be labeled Q and QS I, 1-3, let us say, "infarction." Of these 22, approximately 9 are correct and 13 false-positive diagnoses. One "infarct" will be missed.

In the hospital population (B) approximately 103 cases (11.7 plus 91.0) per thousand subjects will be called "infarct," of which 91 are correct and approximately 12 are false-positive diagnoses. Nine cases of "infarct" are missed.

In table 5 the error ratios for Q and QS I, 1-3 are quite different between a random (1.52) and a hospital population (0.23). A lower error ratio indicates greater "diagnostic accuracy." This difference should be anticipated in the use of the less discriminative Q and QS class II and III patterns (I, 2, and 3).

Results of the application of the single group criterion of Q and QS class I patterns (I, 1) are also found in table 5. The distribution of this item in the "normal" railroad population and the "infarct" group of tables 3 and 4 results in 0.216 per cent false-positive diagnoses, 34 per cent missed "infarcts," and 66 per cent correct "infarct" diagnoses.

In a general population with the composition of group A we find on application of

Table 5

"Diagnostic Error" of Q and QS Items (I, 1-3) in Two Hypothetical *Populations. (A) Random Population of 990 Normal and Ten Old Anterior Infarct Patients (B) Hospital Group of 900 Non-infarct and 100 Old Infarct Patients*

Item	"Random group" (A) False positive	Missed	Correct	Error ratio*
Q and QSI, 1 to 3	12.9	0.9	9.1	1.52
Q and QSI, 1 alone	2.1	3.4	6.6	0.83
Item	**"Hospital group" (B) False positive**	**Missed**	**Correct**	**Error ratio***
Q and QSI, 1 to 3	11.7	9.0	91.0	0.23
Q and QSI, 1 alone	1.9	34.0	66.0	0.54

*The error ratio is the total number of diagnostic errors (false positive in normal subjects plus missed "infarcts") divided by the number of correctly diagnosed "infarcts."

Q and QS I, 1 alone, roughly 9 "infarct" diagnoses per thousand subjects (2.1 + 6.6) of which approximately 7 will be "correct" and 2 false positive, while 3.4 "infarct" cases per thousand subjects will be missed. The diagnostic or discriminative power of this criterion used alone (Q and QS I, 1) is distinctly superior to the broader classification of Q and QS I 1, 2, 3 in application to the general population, but is inferior in application to the hospital population. The restricted criterion Q and QS I, 1 is only slightly better when used as a diagnostic index in a hospital practice as compared to its use in a random population.

This gives a crude picture of the problems in use of any electrocardiographic criterion as an index of disease in population studies, and the general order of magnitude of changes when the criteria are broadened in order to include more "infarcts." The error ratios effectively demonstrate the fact that diagnostic electrocardiographic criteria are more discriminative in populations in which there is a greater prevalence of heart disease. The generalization that accuracy of a diagnostic measure is highly related to the composition of the group to which it is applied has been

Table 6

Classification of the Electrocardiogram in Sixty Cases of Pulmonary Emphysema with No Coronary Heart Disease at Autopsy

Item	Code no.	Per cent of men
Nothing reportable	I, 0	3.3
Q and QS items	I, 1-3	13.3
Axis items	II, 1, 2	26.7
High R waves	III, 1, 2	10.0
S-T depression	IV, 1-3	20.0
T-wave items	V, 1-3	28.3
A-V conduction	VI, 1-4	0.0
Ventricular conduction	VII, 1-4	26.7
Arrhythmias	VIII, 2-6	11.7

made before,[23] but its significance is not yet widely appreciated.

Though 3 groups of individual criteria are used here in Q and QS patterns, since the individual criteria measure different things (different anatomic location), it could be hoped that a reduction of the number of classes might be obtained on further application and study. It is possible that combinations of classes, including Q and QS with T, and S-T classes, might result in improved discriminative power, but this has not been examined. It would be expected that a deeply negative T-wave would strengthen the weaker Q and QS I, 2 and 3 items.

Final combinations, analyses, and diagnostic criteria are to be published in detail with results of studies in several populations. The present classification is proposed now to provide an objective framework for tabulating, analyzing, and reporting electrocardiographic data.

"Specificity" for Coronary Heart Disease

The degree of *specificity* of Q and QS items for "infarction" is not precisely known. Assuming that other manifest heart disease, such as rheumatic mitral stenosis, can be easily eliminated from final tabulations of diagnostic data, it was considered likely that pulmonary emphysema subjects provide the majority of "noncoronary" Q and QS items, such as QS waves and decreasing R amplitude in the precordial leads (I, 1, g; I, 2, g and h). In an attempt to estimate the approximate contribution of emphysema patients to these Q and QS items the electrocardiograms of a well-defined group of severely involved cases were analyzed.

Sixty necropsy cases were selected from 160 hospital files of men with long-standing "asthma" who had emphysema verified by gross necropsy findings. Most were respiratory deaths clinically, and half were good examples of cor pulmonale. No case was accepted with necropsy evidence of acute or healed myocardial infarction, gross or extensive microscopic fibrosis associated with coronary atherosclerosis, valvular heart disease, or prior hypertension (160 systolic, 95 diastolic, or more). Table 6 shows that approximately 13 per cent of this severely involved group are classified in all Q and QS categories and 3 per cent of the total fall into category I, 1.

The particular criterion Q and QS I, 2 (h), decreasing amplitude of R waves from right to left in chest leads, is of considerable interest in regard to the degree of overlapping between emphysema patients, cases of old anterior infarction, and normal subjects. If it were eliminated from the system one would anticipate 3 per cent missed diagnoses of old anterior infarction, based on Q and QS categories in table 4. The finding (Q and QS I, 2 (h) occurred in 10 of that group but as the sole manifestation of old infarction in only 3. There would be no "false positive" diagnoses in "normals," based on the "normal" distribution of table 3. False diagnoses from severe emphysema subjects would be expected, and 6.6 per cent of the subjects in table 6 met this criterion. In the records of the consecutively examined, unscreened railroad-worker sample of table 8, 4 records (0.31 per cent of men) presented decreasing R V_1 to V_3 or V_4 as defined. It was of interest that 3 of the 4 had severe and typical obstructive emphysema, none had a history of myocardial infarction, and 1 had an acute respiratory infection.

Thus, "false positive" labels of "infarction" on the basis of these Q and QS criteria are reduced in final tabulations by excluding

Table 7

Frequency of Electrocardiographic Items, Specified in the Minnesota Code, as Found in Populations of Men Aged 40 to 59 Totally Sampled in Dalmatia and in Slavonia, Yugoslavia, September-December, 1958

Item	Code no.	Dalmatia	Slavonia
Men in area	—	683	719
Resting electrocardiogram	—	669	694
Postexercise electrocardiogram	—	655	673
Q and QS	I, 1	0	3
Q and QS	I, 2	8	7
Q and QS	I, 3	5	3
Axis deviation	II, 1-2	23	39
High R wave	III, 1-2	21	78
S-T items	IV, 1-3	11	20
T items	V, 1-3	9	41
A-V conduction	VI, 1-3	3	3
Ventricular conduction	VII, 1-4	19	10
Arrhythmias	VIII, 1-6	11	12
Postexercise S-T	XI, 1-3	14	41
Postexercise T	XII, 1-3	3	7

Table 8

Frequency of Electrocardiographic Items in the First 1,267 Consecutively Examined U.S. Railway Switchmen, Clerks, and Executives, ages 40 through 59, 1957-1958. (This is not a totally sampled population.)

Item	Code no.	No. of electrocardiographic items
Resting electrocardiogram	—	1,267 (No. of men)
Postexercise electrocardiogram	—	1,158 "
Q and QS	I, 1	18
Q and QS	I, 2	21
Q and QS	I, 3	11
Axis deviation	II, 1-2	43
High R wave	III, 1-2	32
S-T items	IV, 1-3	33
T items	V, 1-3	56
A-V conduction	VI, 1-3	9
Ventricular conduction	VII, 1-4	41
Arrhythmias	VIII, 1-6	4
Postexercise S-T	XI, 1-3	96
Postexercise T	XII, 1-3	19

subjects who meet criteria for chronic lung disease. This holds as well for those with certain valvular heart involvements, but it is inappropriate to write into the classification system numerous exclusions of electrocardiographic items on the basis of clinical findings. These data give some estimation of the magnitude of "noncoronary" sources of particular electrocardiographic findings.

Perhaps unfortunate emphasis has been placed on Q and QS items, which are designed to detect only a small core of "coronary" cases. It is a significant core, however. There is more objectivity and reproducibility in evaluation of this group than for chest pain and "nonspecific" electrocardiographic changes. The prognostic import of other electrocardiographic findings, particularly S-T depression after-exercise, and their validity as indices of coronary artery involvement, are of course, engaging, important considerations.

Another diagnostic assumption must be made in application of such a classification system to different populations, i.e., that electrocardiographic items have the same general import no matter where they are found; that a big Q wave in Yugoslavia has the same meaning as one in Chicago. It is certain that this assumption is not valid in, for example, Brazil, where trypanosomiasis as well as coronary atheroma or thrombosis may cause myocardial necrosis. There may be other examples, and these may not be amenable to exclusion by specific diagnostic tests as can be Chagas' disease. Within this assumption, however, the classification system permits more valid population comparisons.

Findings in "Unknown" Populations

Particular electrocardiographic items of interest are tabulated in tables 7 and 8 for 2 recent surveys. For comparisons between populations the figures are converted to items per thousand subjects, or broken down for exact numbers of individuals with single or specified combinations of electrocardiographic items.

Little more can be said now of the system, either of its reliability or of its diagnostic

validity. It is an attempt to provide a practicable framework for objective comparison of electrocardiographic characteristics of populations, limited to items considered to be of more or less diagnostic or prognostic importance. It is an attempt to improve the reliability of electrocardiographic observations by encouragement of some standard technic of recording, reading, and tabulating electrocardiographic data and by elimination of colloquial differences in terminology and interpretation. It is amenable to modern methods of data processing.

Summary

Information now available about the prevalence and incidence of coronary heart disease is seriously deficient because of the lack of standardized and objective methods of collection, tabulation, interpretation, and reporting of survey data. Chief reliance in the *objective* diagnosis of coronary heart disease rests on the electrocardiogram, a crucial tool in population studies. A classification system for the electrocardiogram in epidemiologic studies has been developed, tested, and herein presented. It is adapted to the usual clinical reading technics of the electrocardiographer. It embodies criteria widely employed and of diagnostic and prognostic import, but *no* stipulations about interpretation are made. The system permits more valid comparisons of data on heart disease between populations. It is susceptible to modern methods of data processing.

Acknowledgment

These individuals have been particularly helpful in giving suggestions and criticism, and in some cases performing independent readings during the development of this system: Christ Aravanis, Ralph L. Brandt, Stanley A. Briller, Dominico Cotrone, Thomas R. Dawber, A. S. Dontas, Joseph T. Doyle, Frederick H. Epstein, Robert P. Grant, Ian T. T. Higgins, Franklin D. Johnston, Aubrey Kagan, W. Kannel, Noboru Kimura, Paul H. Langner, Jr., Huk Yong Ma, W. R. Milnor, Hiroyoshi Mori, Kyoichi Nakagawa, Thomas C. Puchner, Vittorio Puddu, Aaron Shafer, Paul D. White.

The cooperation of Dr. Donald Gleason and Dr. Fred Geisert of the Minneapolis VA Hospital in obtaining necropsy materials is appreciated.

The material for table 7 was gathered and will be published in detail by Dr. Ratko Buzina, Central Institute of Hygiene, Professor Arpad Hahn, Dr. Ivan Mohacek, Dr. Seka Tiefenbach, and Dr. Zvonimir Grgic, Rebro Hospital, Zagreb, Yugoslavia.

Appendix

The Recording

It is apparent from the outset that standardization of diagnostic or reportable criteria depends upon some degree of standardization of recording methods. It has become evident in our studies that, among other factors, different electrocardiographic apparatus, characteristics of the tracing baseline, the paper coordinate system, paper speed, and the number of heart beats recorded, significantly influence the observed values, even when the frequency response of the apparatuses are supposedly similar. High-fidelity, high-speed, multichannel records are not as yet used in U.S. population studies, and are seldom taken in field studies abroad. Agreement on apparatus and technic for epidemiologic studies throughout the world has not been attained, although in the United States standard criteria for leads (I, II, III, aV_R, aV_L, aV_F, V_1-V_6, recorded in the supine position, resting, with 25-mm.-per-second paper speed), instrumentation, and measurements have been well accepted.[24] In recent experiences involving examination of 4,000 subjects in Italy and Finland we have found that multichannel apparatus greatly facilitates the field operation. The recording of strips at 50-mm. paper speed on occasion of doubtful interval measures at 25-mm. speed has significantly improved reading reliability.

In general, the examination program in surveys conducted from this laboratory is such that the resting electrocardiogram is taken after several other stations (interview, history, and physical, etc.) and after lying down for at least 5 minutes. Smoking, eating, and exercise are thus proscribed for at least 1½ hours. A minimum of 4 cardiac cycles per lead is recorded with 5 or 6 beats taken in the left chest leads V_4 to V_6; longer records are made if there is baseline wandering or an arrhythmia. Paper speed is frequently checked by introducing AC interference, and a 1-mv. standardization current is applied on each tracing.

There is no doubt that the yield of reportable electrocardiographic items may be increased by exercise tests and, at least, the prognostic significance of postexercise changes must be evaluated. Steady-state exercise is impractical in field studies but a 3-minute step test is practicable. A single step is employed, usually a strong box made locally and adjusted to 30-cm. height, with a metronome pace of 20 steps a minute. This is much simpler

than a 2-step style and the response and energy expenditure are similar.[25] Chest leads are recorded immediately after exercise in reverse order V_6 through V_2, followed by leads I, II, III, aV_L, and aV_F. As a physician supervises all these recordings he decides whether a 5-minute post-exercise test is to be performed, although this may be routine if desired. A clear-cut clinical or electrocardiographic diagnosis (Q and QS I, 1, or T-wave item V, 1 or 2) of heart disease obviates necessity for an exercise test. Contrary to other recommendations, however, we believe an exercise test is invaluable, and is particularly indicated whenever there are minor or nonspecific or questionable features in the resting electrocardiogram of an otherwise intact subject, and for the evaluation of atypical chest pain. We perform the test in every possible examinee. In over 8,000 examinations we have had only 2 subjects with alarming anginal symptoms and S-T-T changes during and after the exercise. Both occurrences were quite unpredictable with normal resting electrocardiogram and negative history. One subject deliberately withheld his earlier symptomatology and diagnosis to seek confirmation of the opinon of his personal physician, a hazard we had not anticipated.

Current drug therapy, presence or absence of acute infectious illness, and duration of the exercise test if interrupted are noted on the tracing.

Reading Procedures

The criteria derive from many sources familiar to electrocardiographers,[26-35] and are being applied at this time only to men aged 40 and over.

The Q-wave items for leads III and aV_F were assigned to categories of greater and lesser diagnostic significance (I, 1 and 2) on the basis of a study by Weisbart and Simonson.[23] A study of Q and QS items for leads I, II, aV_L, V_{1-6} in a well-defined normal group, hospital populations, and infarct patients, not yet published from this laboratory is the source of some of the Q and QS items herein. There is no evidence that anterior and posterior infarction need be treated separately for epidemiologic purposes, and the Q-wave items pertinent to each have been combined in category I.

If clinical diagnoses rather than the electrocardiographic code are reported in surveys, comparability of data may be maintained if cases labeled "infarct" were identified with reference to the pattern code numbers given. If the diagnosis of infarct is made on some other basis the electrocardiographic evidence should be specified in detail.

For some items no pathology is implied. The criteria for axis deviation are, however, extreme and designed to classify distinctly abnormal axis, beyond the limits for published normal samples.

The criteria for high-amplitude R waves do not include the commonly used criterion of S in V_1 plus R in V_5 greater than 35 mm.,[26] since there was considerable disagreement between electrocardiographers over this criterion. We believe it stands up rather well, however, in that the criterion correlates well with blood pressure in our population studies. Amplitudes in individual leads may be more specific for hypertrophy.

S-T *depression* has been difficult to classify. We are making an extensive breakdown of these categories employing our own more detailed criteria and those of Lepeschkin[34] to determine correlations with clinical and mortality data on follow-up examinations. In this system an S-T depression with "ischemic" contour is given some weight, whereas junctional depression less than 1 mm. with an upward sloping segment is not reported.

In the category of S-T *elevation* it is *not* our intention that routine classification of such elevation be made in populations. There was great variability between observers in reporting this item. Recent myocardial infarction will rarely be encountered in surveys except when hospital patients are involved, and for these it is likely that serial electrocardiograms and other information will be available. The criterion given (IV, 4) simply provides a category in which to document the presence of myocardial "injury" in patients with recent infarct.

T-wave items are, as well, difficult to classify. Many experts believe that myocardial necrosis is indicated by deeply negative T waves as an isolated phenomenon,[35] but this is debated by other experts. There is some general agreement on minus 5 mm. or more as a useful criterion for the classification of these waves, regardless of final pathologic interpretation, which explains the separate categories of V, 1 and 2.

Qualitative Changes

Qualitative findings, such as a slurred downstroke of a QS complex in V_1 and V_2, have import to the experienced clinical electrocardiographer but do not fall into the Q and QS categories herein. It is difficult to describe these changes quantitatively or objectively, and data are not yet available on the degree of overlapping of these items in normal and abnormal populations. The raison d'etre of this classification system is to reduce to a minimum subjective interpretations which enhance observer variability *and* to reduce or at least isolate the items that result in false-positive diagnoses. Items of qualitative, descriptive nature may be entered in miscellaneous categories such as "Qualitative T-wave findings"

(IX, 2) or "QRS abnormalities not mentioned above" (IX, 3).

Ancillary Leads

The question of extra leads and reduced number of leads stimulates varied opinions. It is our opinion that insistence on a reduced number of leads in population studies is being "pound foolish." The small amount of extra time involved in getting a complete record after a subject is wired up is negligible in the light of over-all expenditures of time, energy, and money in serious epidemiologic studies, and the yield of significant Q and QS and S-T, T items is greatly enhanced. There is some validity in the argument for reduced number of leads recorded after exercise, since several vantage points, preferably orthogonal should be recorded rapidly after the exertion. Our data do not allow us to solve this question. We pay little regard to aV_R in studies of adult populations and do not object to an "11 lead" electrocardiogram, but omitting a position in normal rotation on the switch may cause confusion in technicians' conditioned reflexes.

Our experience with electrically orthogonal, weighted lead systems involving only 3 leads, X, Y, Z (SVEC III system)[36] has given us some hope that the number of electrocardiographic leads may eventually be reduced. In practice, however, the distortion in conventional lead systems may be advantageous in recognition and empirical classification of pathologic conditions of the myocardium.

If final clinical classifications of coronary heart disease are based on leads other than I, II, III, aV_R, aV_L, aV_F, V_1-V_6 it should be so stated in reporting the data. We have set up the following routine for recording extra leads, and tabulate the presence of a Q duration of 0.04 second or more, or a QS pattern in the appropriate ancillary lead (code I, 2 i), taking into consideration the "normal Q area" distribution.[30, 32] This routine presupposes a physician interpreting records on the spot in the field.

a. Take extra lead V_7 to V_9 *when* a predominately upright QRS does not appear in V_6 or in suspect lateral infarct.

b. Take extra lead V_x (ensiform) *when* there is a QS in V_1 and V_2 or V_1 through V_3, *and* V_{3R}, *and* V_1 through V_3 at *level of* fifth intercostal space at sternum.

c. Take extra lead V_4 through V_7 at *level of* third and fourth intercostal space at midclavicular line *when* there is suspect high lateral infarct.

Definitions

1. Baseline reference levels and intervals are read according to recommendations of the American Heart Association Criteria Committee[25]:

P amplitude from T or U-P interval.
QRS amplitudes from P-R interval at onset of QRS.
T amplitude from T or U-P when possible otherwise the level of trace at the beginning of QRS.
P-R interval is the longest in any limb lead.
QRS duration is the longest in any limb lead.

2. A Q wave must be 1 mm. deep followed by an R wave of 1 mm.

3. An initial R wave must be a definite departure above the P-R baseline, not simply a lift or rising slope of the P-R baseline.

Reading of Intervals and Amplitudes

Beat-to-beat variability of interval measurements is troublesome. In practice it is helpful to require that a *majority* of beats recorded for the particular lead meet the critical duration criterion. Longer and 50-mm.-per-second strips aid materially in this regard and occasionally measurements from the postexercise record may elucidate a questionable item. As a rule, however, all Q and QS items, R amplitudes, etc., are measured in the resting electrocardiogram.

Q and R waves under 1-mm. amplitude are read with poor reliability in direct-recorded tracings at 25-mm.-per-second paper speed. The lack of adequate data on large Q/R ratio or wide Q duration in over-all low-amplitude QRS complexes has led us to the arbitrary, but practicable minimum criteria for Q and R amplitudes spelled out in the classification system.

Mean heart rate from leads I and V_6 of the resting record are employed for the criteria of tachycardia and bradycardia.

The criteria for amplitude of decreasing R waves from V_1 to V_4 is derived from our own studies in infarct and normal groups. Others have reported the interesting differences between observers in labeling of QS complexes, or absent initial R waves.[30] A full 1-mm. R wave is not necessary in the calling of an *initial* R wave, but a distinct sharp R deflection rising above the P-R baseline is required, not simply an ascending slope or terminal lift in the P-R segment.

The criteria for S-T depression give fair reliability between readers by considering these principles:

1. S-T depression is placed in a questionable category or not tabulated when found in less than a majority of beats of the lead, when the baseline is swinging widely or sloping up or down, and when the S-T segment describes an arc with no clear junction with QRS.

2. The junction (J) is taken at the end of QRS activity rather than at arbitrary points in the mid-arc or from the point of transition from very rapid to less rapid potential changes.[37]

3. S-T depression is read from the P-R segment baseline at the beginning of QRS.

4. The postexercise S-T depression criteria refer to an absolute value and not to a change relative to the resting level.

Recording of long lead strips, with careful attention to obtain level baselines, is constantly sought, but not always attained.

The Classification

Findings are reported only when they appear in leads designated on the right-hand side of the classification below. "I, II, V_2–V_6" means *any* of leads I, II, $V_{2, 3, 4, 5, \text{ or } 6}$. "$V_1$ through V_4" means *all* of leads V_1 through V_4. A positive finding in *any* of the designated leads is reportable *unless* otherwise stipulated. Within each major category (Roman numeral) only the most significant deviation is reported (generally the lowest Arabic numeral). A finding that meets a criterion only in a single complex and therefore might be an artifact or expression of beat-to-beat variation is not reported as positive. Amplitudes refer to a calibration of 1 cm. = 1 mv.

Code for Resting Electrocardiograms

Col.	Punch	Category	Leads
0	0	Blank—no electrocardiogram available	
I	0	No herein reportable electrocardiographic items	
		Q and QS patterns (Q must be 1 mm. or more with associated R of 1 mm. or more)	
	1	Class I (any of a through g)	
		a. Q/R=1/3 or more *and* Q duration=0.03 sec. or more	I, II, V_2-V_6
		b. Q duration=0.04 sec. or more	I, II, V_1-V_6
		c. Q duration=0.04 sec. or more *and* R amplitude 3 mm. or more	aV_L
		d. Q duration=0.05 sec. or more *and* a Q wave present in aV_F	III
		e. Q duration=0.05 sec. or more	aV_F
		f. QS pattern when R wave is present in adjacent precordial lead to the right	V_2-V_6
		g. QS pattern	V_1 through V_4 V_1 through V_5 V_1 through V_6
	2	Class II (any of a through i)	
		a. Q/R=1/5 to 1/3 *and* Q duration=0.03 sec. or more	I, II, V_2-V_6
		b. Q duration=0.03 to 0.04 sec.	I, II, V_2-V_6
		c. Q duration=0.03 to 0.04 sec. *and* R amplitude 3 mm. or more	aV_L
		d. Q duration=0.04 to 0.05 sec. *and* a Q wave present in aV_F	III
		e. Q duration=0.04 to 0.05 sec.	aV_F
		f. Q amplitude=5 mm. or more	III, aV_F
		g. QS pattern and absence of code VII_1	V_1 through V_3
		h. Decreasing absolute R amplitude *and* smallest R=2 mm. or less *and* absence of code III_2 or $VII_{2,3}$	V_1 through V_3, V_4
		i. Q duration=0.04 sec. or more or a QS pattern	(Ancillary leads, see text)
	3	Class III (any of a through c)	
		a. Q/R=1/3 or more *and* Q duration less than 0.03 sec.	I, II, V_2-V_6
		b. QS pattern *and* absence of code VII_1 or III_1	V_1 and V_2
		c. Q/R=1/5 to 1/3 *and* Q duration less than 0.03 sec.	I, II, V_2-V_6
II		*QRS axis deviation*	
	1	Left	
		QRS axis = −30° or greater	I, II, and III
	2	Right	
		QRS axis = +120° or greater (The algebraic sum of major positive and major negative waves must be negative in I, positive in III, and in I must be one half or more of that in III)	I, II, and III
III		*High amplitude R waves*	
	1	Left	
		R more than 26 mm.	V_5, V_6
		R more than 20 mm.	I, II, III, aV_F
		R more than 12 mm.	aV_L
	2	Right	
		QRS duration less than 0.12 sec. *and* R amplitude=5 mm. or more *and* R/S ratio=1.0 or more *and* QRS transition zone or decreasing R/S to left of V_1. (Includes incomplete RBBB which meets above criteria)	V_1
IV		*S-T junction and segment* (Measured from preceding P-R interval at onset of QRS)	
		Depression:	
	1	S-T-J depression 1 mm. or more	I, II, aV_L, aV_F, V_1-V_6
	2	S-T-J depression 0.5-0.9 mm. *and* S-T segment horizontal or downward sloping	I, II, aV_L, aV_F, V_1-V_6
	3	No S-T-J depression as much as 0.5	

Col.	Punch	Category	Leads
		mm. but S-T segment sloping down and reaching 0.5 mm. or more below P-R baseline	I, II, aV_L, aV_F, V_1-V_6
		Elevation: (Not routinely applied, see text)	
	4	S-T segment elevation of 1.0 mm. or more	I, II, III, aV_L, aV_F, V_5, V_6
		2.0 mm. or more	V_1-V_4
V		*T-wave items*	
	1	T amplitude=minus 5 mm. or more	I, II, V_2-V_6
		when R amplitude=5 mm. or more	aV_L
		when QRS mainly upright	aV_F
	2	T amplitude=minus 1 to 5 mm.	I, II, V_2-V_6
		when R amplitude=5 mm. or more	aV_L
		when QRS mainly upright	aV_F
	3	T wave flat or small diphasic (negative phase less than 1 mm.)	I, II, V_2-V_6
		when R amplitude=5 mm. or more	aV_L
		when QRS mainly upright	aV_F
VI		*A-V conduction*	
	1	Complete A-V block (permanent or intermittent)	any
	2	Partial A-V block	any
	3	P-R interval over 0.21 sec. (*any* heart rate)	I, II, III
	4	Accelerated conduction (''Wolff-Parkinson-White'')	any
VII		*Ventricular conduction*	
	1	Left bundle-branch block (LBBB): QRS duration 0.12 sec. or greater in	I, II, III
		and R peak duration 0.06 sec. or more in any of	I, II, aV_L, V_5, V_6
	2	Complete right bundle-branch block (RBBB): QRS duration 0.12 sec. or greater in	I, II, III
		and R prime greater than R in	V_1
	3	Incomplete RBBB: R prime greater than R *and* QRS duration less than 0.12 sec. (report under III_2 if those criteria are met)	V_1
	4	Intraventricular block: QRS 0.12 sec. or more *and* no LBBB or RBBB pattern	I, II, III
VIII		*Arrhythmias*	
	0	Any combination of arrhythmias below (for punch card purposes)	
	1	Frequent (4 or more in 40 complexes) premature atrial, nodal, or ventricular beats	
	2	Ventricular tachycardia (over 100/min.)	
	3	Atrial fibrillation or flutter	
	4	Supraventricular tachycardia	
	5	Ventricular (idioventricular) rhythm (up to 100/min.)	
	6	A-V nodal rhythm (up to 100/min.)	
	7	Sinus tachycardia (over 100/min.)	
	8	Sinus bradycardia (under 50/min.)	
	9	Arrhythmias not mentioned above	
IX		*Miscellaneous*	
	0	Combinations below of item 2 or 3 with item 1, 2, 3, 4, 5, or 6 (for punch card purposes)	
	1	Low QRS amplitude (in I, II, III no positive or negative deflection over 5 mm. *or* maximum QRS amplitude less than 10 mm. in V_1-V_6)	
	2	''Qualitative'' T-wave findings including ''high'' or peaked T, postextrasystolic T-wave inversion, T notching, etc.	
	3	QRS findings not mentioned above including notching, slurring, RR prime, rotation, or others	
	4	Prolonged Q-T interval (evaluated from kQT)	
	5	P wave findings including peaked, negative, 3 mm. amplitude or over, or others	
	6	Negative U wave in V_3-V_6	
	7	Other items not mentioned above	
	8	Questionable category due to technical imperfections in record or beat-to-beat variability of measurement	
	9	Combinations above of item 7 or 8 with item 1, 2, 3, 4, 5, or 6 (for punch card purposes)	

Code for Postexercise Records

Col.	Punch	Category
X		*Exercise test*
	1	No exercise test made
	2	Exercise test stopped
	3	Exercise test completed
XI		*S-T items postexercise*
	1	Change from *no* coded S-T item at rest to S-T item type IV, 1 postexercise
	2	Change from *no* coded S-T item at rest to S-T item type IV, 2 postexercise
	3	Change from *no* coded S-T item at rest to S-T item type IV, 3 postexercise
	4	Change from one coded S-T item at rest to a lower numerical S-T item postexercise (IV, 3 to type IV, 1, etc.)
	5	Change from one coded S-T item at rest to a higher numerical item postexercise (IV, 1 to type IV, 3, etc.)
	6	No change from resting coded S-T item
	7	Change from *any* coded S-T item at rest

Col.	Punch	Category
		to *no* reportable S-T item postexercise
	8	Questionable S-T depression postexercise due to technical considerations
XII		*T items postexercise*
	1	Change from *no* coded T item at rest to T item type V, 1 postexercise
	2	Change from *no* coded T item at rest to T item type V, 2 postexercise
	3	Change from *no* coded T item at rest to T item type V, 3 postexercise
	4	Change from one coded T item at rest to a lower numerical T item postexercise (V, 3 to type V, 2, etc.)
	5	Change from one coded T item at rest to a higher numerical T item postexercise (V, 2 to type V, 3, etc.)
	6	No change from resting coded T item
	7	Change from *any* coded T item at rest to *no* reportable T item postexercise
	8	Questionable T item postexercise due to technical considerations
XIII		*A-V conduction, postexercise*
	1	Change from *no* coded A-V conduction item at rest to complete A-V block postexercise
	2	Change from *no* coded A-V conduction item at rest to partial A-V block postexercise
	3	Change from *no* coded A-V conduction item at rest to P-R interval more than 0.21 sec. postexercise
	4	Change from *no* coded A-V conduction item at rest to accelerated conduction
	5	Change from one coded A-V conduction item at rest (VI, 1-4) to another A-V conduction item postexercise
	6	No change from resting coded A-V conduction item
	7	Change from *any* A-V conduction item at rest to *no* A-V conduction item postexercise
XIV		*Ventricular conduction, postexercise*
	1	Change from *no* coded ventricular conduction item at rest to left bundle-branch block (LBBB)
	2	Change from *no* coded ventricular conduction item at rest to complete right bundle-branch block (RBBB)
	3	Change from *no* coded ventricular conduction item at rest to incomplete right bundle-branch block
	4	Change from *no* coded ventricular conduction item at rest to intraventricular block
	5	Change from one coded ventricular conduction item at rest (VII, 1-4) to another ventricular conduction item postexercise
	6	No change from resting coded ventricular conduction item
	7	Change from *any* ventricular conduction item at rest (VII, 1-4) to *no* ventricular conduction item postexercise
XV		*Arrhythmias, postexercise*
		(exclude VIII, 7-8, sinus tachycardia and bradycardia)
	1	Change from *no* coded arrhythmia at rest to *any* reportable arrhythmia postexercise
	2	Change from one coded arrhythmia at rest to another arrhythmia postexercise
	3	No change from coded resting arrhythmia
	4	Change from *any* arrhythmia at rest to *no* arrhythmia postexercise
XVI		*Miscellaneous, postexercise*
	1	Change postexercise to any item not mentioned above

Code for Serial Electrocardiograms

Serial electrocardiograms will rarely be available in ordinary cross-sectional surveys but their utilization in longitudinal studies must be considered. Major serial changes will be apparent by comparing the classification according to the present system from the same persons on different occasions. In order to note the findings in such serial comparisons, it is suggested to add another category, and column, for the punch code, as follows:

XVII		*Serial changes, general*
	1	Change from item I, 0 to *any* reportable item I-XVI
	2	Change in *any* reportable item I-XVI
	3	No change in coded item
	4	Change from *any* item I-XVI to *no* reportable item
	5	No serial comparison available
XVIII		*Q and QS items, serial changes*
	1	Change from one coded Q and QS item to a lower numerical Q and QS item (I, 3 to I, 2, etc.)
	2	Change from one coded Q and QS item to a higher numerical Q and QS item (I, 1 to I, 2, etc.)
	3	No change in coded Q and QS item
	4	Change from *no* coded Q and QS item to Q and QS item I, 1
	5	Change from *no* coded Q and QS item to Q and QS item I, 2
	6	Change from *no* coded Q and QS item to Q and QS item I, 3
	7	Change from *any* coded Q and QS item to *no* reportable Q and QS item

Col.	Punch	Category
XIX		*S-T items, serial changes*
	1	Change from one coded S-T item to a lower numerical S-T item (IV, 3 to IV, 1, XI, 3 to XI, 1, etc.)
	2	Change from one coded S-T item to a higher numerical S-T item (IV, 1 to IV, 2, XI, 2 to XI, 3, etc.)
	3	No change in coded S-T item
	4	Change from *no* coded S-T item to S-T item type IV, 1, rest or postexercise
	5	Change from *no* coded S-T item to S-T item type IV, 2, rest or postexercise
	6	Change from *no* coded S-T item to S-T item type IV, 3, rest or postexercise
	7	Change from *any* coded S-T item to *no* reportable S-T item
XX		*T items, serial changes*
	1	Change from one coded T item to a lower numerical T item (V, 3 to V, 1, XII, 3 to XII, 1, etc.)
	2	Change from one coded T item to a higher numerical T item (V, 2 to V, 3, XII, 2 to XII, 3, etc.)
	3	No change in coded T item
	4	Change from *no* coded T item to T item type V, 1, rest or postexercise
	5	Change from *no* coded T item to T item type V, 2, rest or postexercise
	6	Change from *no* coded T item to T item type V, 3, rest or postexercise
	7	Change from *any* coded T item to *no* reportable T item
XXI		*Blocks, serial changes*
	1	Change from *no* coded A-V block to *any* A-V block (VI, 1-4)
	2	Change from *any* coded A-V block to *no* A-V block
	3	No change in A-V block
	4	Change from *no* coded ventricular conduction defect to *any* ventricular conduction defect (VII, 1-4)
	5	Change from *any* coded ventricular conduction defect to *no* ventricular conduction defect
	6	No change in ventricular conduction defect
XXII		*Arrhythmias, serial changes* (exclude VIII, 7-8, sinus tachycardia and bradycardia)
	1	Change from one coded arrhythmia to another (VII, 1-6)
	2	Change from *no* coded arrhythmia to *any* reportable arrhythmia
	3	No change in coded arrhythmia
	4	Change from *any* coded arrhythmia to *no* reportable arrhythmia

Changes in items other than those provided for above (i.e., other than Q and QS, S-T, T, blocks and arrhythmias) would be cumbersome to record in a formal classification code. But note that the fact of such miscellaneous changes can be ascertained by a record (punch) of a change in column XVII accompanied by no record of change in columns XVIII through XXII.

Summario in Interlingua

Le currentemente disponibile informationes con respecto al prevalentia e al incidentia de morbo cardiac coronari es gravemente inadequate a causa del absentia de methodos standardisate e objective de collection, tabulation, e publication de constatationes epidemiologic. Le diagnose *objective* de morbo cardiac coronari depende primarimente del electrocardiogramma que es un instrumento indispensabile in studios de dimensiones demographic. Un systema de classification pro le electrocardiogramma in studios epidemiologic ha essite disveloppate e testate e es presentate in iste articulo. Illo es adaptate al usual technicas de lectura clinic que es in uso in le practica routinari. Illo imbracia criterios que es extensemente empleate e que es de importantia diagnostic e prognostic, sed nulle stipulationes es facite con respecto a questiones interpretatori. Le systema premitte plus valide comparationes del datos cardiopathologic pro varie populationes. Illo es adaptabile a moderne methodos de mechano-manipulation de datos.

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SYMPOSIUM ON REGULATION OF THE CARDIOVASCULAR SYSTEM IN HEALTH AND DISEASE

Guest Editor: LYSLE H. PETERSON, M.D.

Regulation of Blood Volume

By E. B. REEVE, B.M., B.Ch.

IS THERE any evidence that the blood volume is regulated? Or, put more specifically, is there any evidence that signalling systems, nervous or hormonal, respond to changes in the optimal level of blood volume and bring into play mechanisms that restore the blood volume to optimal levels? By examining what is known of the factors controlling blood volume we may see if any answer can at present be given to this question.

Table 1 shows that the average healthy adult man has about 2 liters by volume of red cells (in number about 2×10^{13}) and 3 liters of plasma. In a given healthy adult these values remain fairly constant, rarely varying by more than 5 to 10 per cent about a mean value over periods of weeks or months. Table 1 also shows approximate estimates for the volume of the red marrow. It has been calculated that the red marrow contains about 7×10^{11} red cell precursors, or approximately 3 per cent of the number of the circulating red cells.[2] Many of the precursor cells, however, are a good bit larger than the mature red cell, so that, at a guess, we may take the volumes of the red cell precursors in the bone marrow to be about 5 per cent of that of the circulating red cells. This volume is only a small fraction of the red cell volume.

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This paper is a general account of some of the material in a review by Drs. T. H. Allen, J. E. Roberts and the author.[1]

Supported by a grant (H-2262) from the National Heart Institute, U. S. Public Health Service, and by a grant from the Colorado Heart Association.

Is there any need for the blood volume to be maintained with any degree of constancy? What would go wrong if it decreased or increased greatly? The function of the circulation is the adequate perfusion of the tissues so that nutrients—gases and solutes—may be delivered and waste products may be removed. For this function the most important parts are the capillaries and the blood perfusing them, and the heart and the larger blood vessels, which pump and distribute the blood to the capillaries, are only servants in this system. It seems probable that the capillaries contain only a small per cent of the circulating blood, although no precise estimates of this quantity have ever been made and, therefore, we can rephrase our question thus: can the heart and the distributing blood vessels maintain an adequate perfusion of the tissues with large changes in blood volume? It is known that withdrawing 500 ml. (about 10 per cent of the blood volume) from an adult man has little effect, and in *supine* man a reduction of the blood volume by even 15 to 20 per cent may not apparently greatly embarrass the circulation. A reduction of the blood volume by 30 per cent, 1,500 ml., leads to a fall in blood pressure,[3] and by 30 to 40 per cent to a fall in cardiac output and an increase in circulatory resistance, with signs of inadequate tissue perfusion, such as increased blood carbon dioxide and lactic acid content.[4] There is little good evidence on how much the blood volume may be increased without circulatory disturbance. Our own observations show that the blood volume of the

Table 1

Adult Man	
Blood volume	5 liters
Red cell volume	2 liters
Plasma volume	3 liters
Erythroid marrow	? 100 ml.

rabbit may be increased by 50 per cent over a week or so by dextran infusions, without apparently seriously embarrassing the circulation; but an increase greater than this may lead to pulmonary congestion, pleural effusions, cyanosis, dyspnea, and death on exertion. Patients with congestive cardiac failure rarely show increases in blood volume greater than 1.5 to 2.5 liters.[5] It can perhaps be concluded that circulatory function is little disturbed by changes in blood volume of ± 10 per cent, but is seriously disturbed by reductions of 30 per cent or increases of perhaps 50 per cent. Though this does not suggest that an existing regulation of the blood volume needs to be very precise, it does indicate that the blood volume cannot depart too far from its normal level.

Let us now turn to an examination of some of the controlling mechanisms. First we examine some properties of what may be called "flux systems." These are systems, linked or otherwise, through which there is continuous flow of materials. Figure 1 shows a chain of simple flux systems. Consider the topmost of these. It consists of a tank containing a volume, V_1, of fluid with a tap controlling the inflow, and another tap controlling the outflow. V_1, the volume in the tank, depends on the rates of inflow and outflow. For instance if the inflow remains constant, opening the outflow tap ("outflux 1") further will cause V_1 to decline until a new equilibrium is reached, and reducing the outflow will cause V_1 to increase. If the outflow is held constant, increasing or decreasing the inflow by the "influx" tap will cause V_1 to increase or decrease until new equilibria are reached. Thus, the volume V_1 is controlled by the settings of the taps "influx" and "outflux 1." Now, examine the further degree of complexity obtained

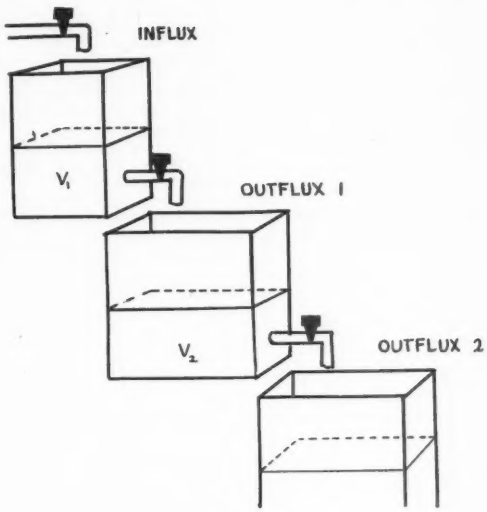

Figure 1

A chain of simple flux systems. Each flux system consists of a tank containing a volume of fluid through which there is continuous flow. Inflow is governed by an inflow tap and outflow by an outflow tap, and the volume in the tank depends on the settings of these taps.

when the top tank empties into a second tank, containing V_2 volume of fluid, the outflow from which is governed by tap "outflux 2." What controls the volume of V_2? Clearly taps outflux 1 and outflux 2, but how effective is the former? If outflux 1 is opened fully, we can suppose that the contents of tank 1 rapidly flow into tank 2. This will temporarily increase the volume V_2, but this in turn will increase the outflow through outflux 2, so that V_2 will then start declining, and now the inflow to the second tank is governed by the inflow to the first tank. This illustrates that the real governors of a system in equilibrium such as that of figure 1 are the first inflow and the last outflow taps, provided of course that there is continual flow through the system. Changing the setting of intermediate taps can only have temporary effects.

The red cell volume may be pictured as a flux system contained in a tank, the blood vessels and heart, with an inflow tap from the erythropoietic bone marrow, and an outflow

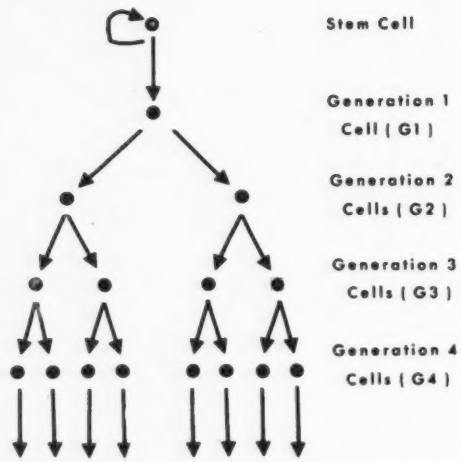

Figure 2

A possible scheme of the division of the erythrocytic precursor cells in the bone marrow. To avoid the complexities of the various nomenclatures the initial cell in the series is termed the stem cell and cells formed by division from this: generation-1, generation-2, generation-3, and generation-4 cells.

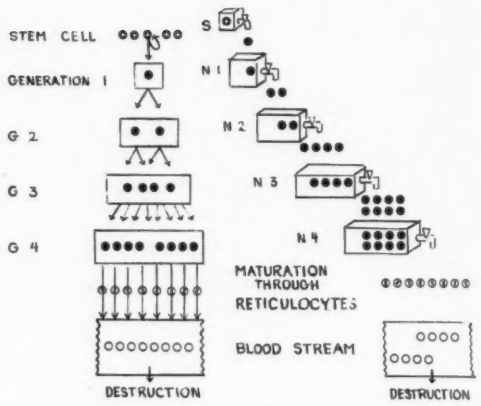

Figure 3

The left side of the figure presents the division of the erythrocyte precursors shown in figure 2. The right side of the figure pictures these divisions as a chain of interlinked flux systems of the kind shown in figure 1. The total numbers of stem cells, S, and each generation, N1 for G1, N2 for G2, N3 for G3, and N4 for G4, are represented as each occupying a tank. As each cell divides, it leaves the tank it is in and passes to the next tank. This is a pictorial representation of mathematical relations developed elsewhere.[1]

tap, the flow of which represents the rate at which red cells are removed from the circulation. In healthy man red cells live for about 100 days after entering the circulation, so ordinarily the events of 100 days earlier control the setting of the outflow tap—clearly not a precise controlling mechanism. Any precise control of the red cell volume must therefore depend on the inflow tap, which is the rate of formation of red cells by the bone marrow.

The formation of red cells in the bone marrow can be represented by something like the events shown in figure 2.[6] Some cell, call it the stem cell, the first in the erythroid series, must divide, and to maintain the supply of stem cells it seems likely that one of the daughter cells, call them generation 1 (G1) cells, must persist as a stem cell, and the other must become a true first-generation cell. The first-generation cell must divide again to form 2 generation-2 cells, these must both divide again to form 4 generation-3 cells, and so on, until finally in this process division ceases and the cells mature through the stage of the reticulocyte by losing their nuclei to become new red cells. Although there has been much study of the morphology of the bone marrow, at present we do not know exactly how many generations there are between the division of the stem cell and the red cell, but a reasonable guess is 4, which would mean that each stem cell division led to the production of 8 red cells. Drs. Allen and Roberts[1] have developed equations to describe this system, which are visually presented in figure 3. The left side of the figure pictures the division process as already described. The right side of the figure pictures the results as a train of interlinked flux systems. The first (topmost) tank contains all the stem cells in the bone marrow, and we imagine these as self-replenishing by the unusual division process described above. Of the pair of cells formed by division of these, one passes back into the tank as a stem

cell, the second becomes a generation-1 (G1) cell and leaves the first tank to enter the second tank, which contains all the G1 cells, N1 in number. The outflow from this tank consists of the generation-2 cells (G2); that is, as soon as the G1 cells divide, they are pictured as leaving the generation-1 tank and entering the generation-2 tank. Note that twice the number of cells leave the generation-2 tank as enter. The G2 cells divide to become G3 cells, so that there is a generation-3 tank with an inflow of divided G2 cells, and finally there is a generation-4 tank. Thereafter, although the red cells change their morphology through the reticulocyte stage, no further division takes place. In the light of our previous discussion 2 points are clear from figure 3. First the governor of the system is the first inflow, the rate of division of the stem cells. Second, though we might expect temporary changes in red cell volume from, say, opening one of the intermediate taps widely, which is equivalent to speeding up the division of an intermediate generation, such an effect can only be temporary, and because of the relatively small volume of the erythropoietic bone marrow, quite small.

Figure 4 shows a regulated flux system, regulated in the sense defined in this symposium. Both inflow and outflow taps are controlled by regulating systems. These are pictured as consisting of a receptor (R), which signals the level of the volume in the system to an integrator (I), where it is compared with an ideal signal, S. The ideal signal in servo-engineering is often termed the goal-setter. The difference between the incoming signal and the ideal signal, E, termed the "error" in servo-engineering, then activates an effector, M, pictured in figure 4 as a servomotor, which turns the inflow or outflow tap, or both, to change the volume to a more optimal level. Can we fit our present knowledge of the regulation of the red cell volume into such a system? Our discussion has ruled out the outflow tap as being in any way a precise controller, and has shown that the prime regulator of the inflow, M, the servomotor shown, must be the rate of division of the stem cells.

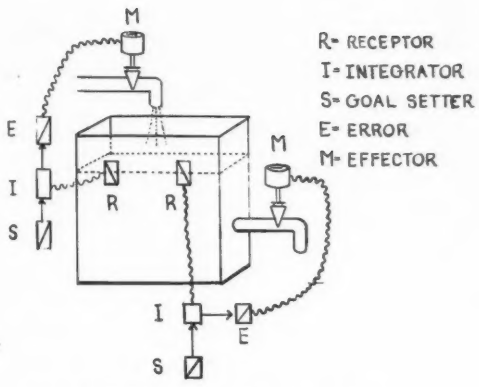

Figure 4

A regulated flux system. The regulation of inflow and outflow is pictured as controlled by servomechanisms. Each of these consists of a receptor mechanism, R, which senses the volume of fluid in the tank. This signals an integrator, I, which compares the signal with an ideal signal from a goal-setting mechanism, S. The resulting integrated output from the integrator, the "error," E, then activates an effector system, M, pictured as a servomotor, which controls the setting of the tap.

This suggests that the error system works through some humoral cell growth and division factor. Evidence partially supports this. Thus, it has long been known that exposure of a mammal to low oxygen tension results in an increase in red cell volume. For instance, moving adult men from sea level to 15,000 feet leads to an increase in red cell volume over some months to some 1.5 times the initial level.[7] Clearly the stem cell tap must have been widely opened, since no change occurs in the length of red cell life. If one member of a pair of surgically joined rats (parabiotic rats) is exposed to a low oxygen tension, not only the red cell volumes but also the bone marrows of both animals show the changes expected on exposure to low oxygen tension, strongly suggesting the liberation of a humoral growth factor.[8] In the last few years much work has been done on such factors, the so-called erythropoietins; but much of this work is incomplete because the effects of supposed hormones *on the stem cell system* have

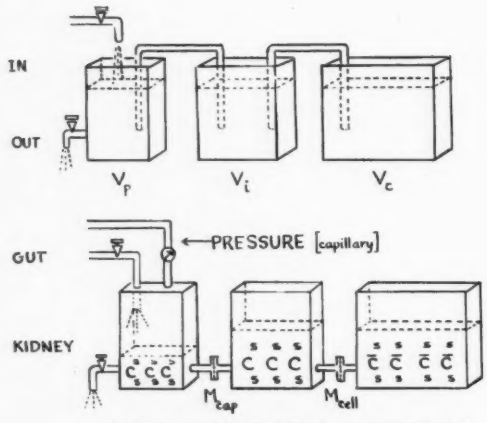

Figure 5

Top. *The elements of a model of body water consisting of 3 tanks, V_p representing plasma water, V_i interstitial water, and V_c cellular water. A controlled flux passes through the tank, V_p. The tanks are not drawn to scale.* Bottom. *Further details have been added to the model in the upper figure. These are a pressure to represent the mean capillary pressure, semipermeable membranes, M_{cap} to represent the capillary membranes, and M_{cell} to represent the cell membranes, and solutes, s, representing the crystalloids, C representing the plasma colloids, and $\bar{C}$ the cell colloids.*

not been studied. We can at present only conclude that the controller, M, of the inflow tap is probably some hormone or hormones. What however of the sites and nature of the receptors that signal the state of the red cell volume, and the nature of the integrating device and the goal-setter? Of these we are at present entirely ignorant.

Let us now turn to the question of the regulation of the plasma volume, which in health forms the other three fifths of the circulating blood volume. For clarity we shall first develop a model of the factors controlling the plasma volume and then discuss whether there is regulation of the plasma volume acting through *some* of these controls. The remainder of the controlling systems falls into the province of Dr. Elkinton's paper.

First, 93 per cent of the volume of plasma is water, and we therefore disregard the other 7 per cent made up of the plasma proteins, and fats. We require a model, that is a simplified picture, preferably capable of mathematical expression, of the factors responsible for the level of the plasma volume. The body water can be divided into plasma water, interstitial water, and cell water, and the upper part of figure 5 shows the elements of a model, consisting of 3 tanks, representing plasma water, V_p, interstitial water, V_i, and cell water, V_c, joined together by siphons, with a flux passing through the plasma water tank. The inflow is primarily from the alimentary tract and the controlled outflow chiefly through the kidneys, though water loss also occurs through the skin and lungs. The tanks are not drawn to scale, and there is relatively much less plasma water and more cell water than shown. Also, for the tanks to be anything like the body water there must be a continuous rapid exchange through the siphons in both directions. For we know that labeled water introduced into the body rapidly exchanges with all the body water, primarily by carriage in the circulation and diffusion through the tissue fluids and cells.

The lower part of figure 5 shows further details of the model. First, semipermeable membranes have been placed between the plasma and the interstitial fluids, M_{cap}, (to represent the capillary membrane) and between the interstitial and cellular fluids, M_{cell}, (to represent the cellular membranes). The capillary membrane allows free passage of water and salts and very slow passage of the proteins; the cell membrane allows, we suppose, only free passage of water, other substances passing across it requiring "active transport." Next, solutes have been added, large solutes—the colloids,—shown by C's, and smaller solutes,—the crystalloids—shown by s's. The main crystalloids in the extracellular fluids (the plasma and interstitial fluids) are the sodium salts of chlorides and bicarbonates, and the main colloids, the plasma proteins, which are on the average 3 to 5 times more concentrated in the plasma than in the interstitial fluid. The main crystalloids in the cellular fluid are potassium and magne-

sium salts, but little is known of the cell colloids. The body fluids are not all at the same pressure. This is particularly true for the plasma, which is exposed to a series of pressure gradients generated by the action of the heart and the distensibility of the blood vessels. In the model the only pressure considered is the average pressure at the capillary membranes, and this is pictured in figure 5 as generated by a pressure system (for instance a tank of compressed air) and measured by a pressure gage. A final point about the model needs emphasizing: the distribution of water in the tanks depends on the distribution of the crystalloids and colloids through their effects on the rate of diffusion of water. Thus, suppose more solute is added to one of the tanks and the membrane separating it from the next tank impedes the passage of the added solute. Then the added solute will reduce the rate of diffusion of the water to which it has been added, and water will diffuse inwards more rapidly than it diffuses outwards, until either a restraining pressure is developed, the osmotic pressure, or eventually the solutes are evenly distributed among the tanks. (This is only strictly true if Donnan forces are negligible.) In either case at equilibrium the rates of diffusion across the membrane will be equal in both directions.

Examining figure 5, we can now come to certain conclusions about the factors controlling plasma volume. 1. The volume of plasma water will depend on the quantity of the total body water, which must be controlled chiefly by the rates of inflow and outflow through the gut and kidney. 2. For a given quantity of body water, the volume of plasma water must depend on the factors controlling the distribution of water among the 3 tanks. These are (2a) the *capillary pressure*—a higher pressure will displace water out of the plasma tank by increasing the outward diffusion rate; (2b) the *plasma colloid*—secretion of more protein into the plasma will counteract water outflow to the other compartments by reducing the rate of water diffusion outward; (2c) the quantities of *crystalloid solutes* in the extracellular and cellular fluids. For instance, it can be shown experimentally that introduction of hypertonic saline into the plasma leads to passage of water from the cells into the extracellular fluids. Factors (2a) and (2b) it will be remembered were proposed by Starling many years ago.

Dr. Elkinton in the following article deals with the control of (1) and (2c). It may be noted that the quantities of crystalloid solutes in the body depend on crystalloid inflow and outflow in the same way as body water depends on water flux; the distribution of crystalloid solutes in the body depends on cellular activity as is shown by the redistributions that occur on cell death. Certain of the crystalloids, for instance, sodium in the bones, also exist in stores in the body so that the quantity in the body fluids can be modified by release from or deposition in the stores, though little is known of the control of such exchanges.

Dealing with the remaining factors, we cannot at present say whether any *regulation* of mean capillary pressure or of plasma colloid osmotic pressure (protein concentration) exists. Something has been learned of the factors controlling the total quantity of circulating plasma proteins. Eighty to ninety per cent of the plasma proteins, that is essentially all but the immune gamma globulins, are synthesized in the liver.[9, 10] Synthesis is continual as is breakdown, so that, as with the red cells, the total quantity of a given plasma protein can be pictured as part of a flux system, with continual inflow from the liver and outflow to the breakdown site. In an adult man about 10 Gm. of albumin is made and broken down a day, and it can be calculated that a single liver cell makes about 5,000 albumin molecules per second. It seems likely that the amino acids, which are joined together to make these proteins, are assembled on nucleic acid protein "assembly lines" and that these form part of a network through the cell known as the endoplasmic reticulum.[11] The sites of plasma protein breakdown and the factors controlling the rate of breakdown

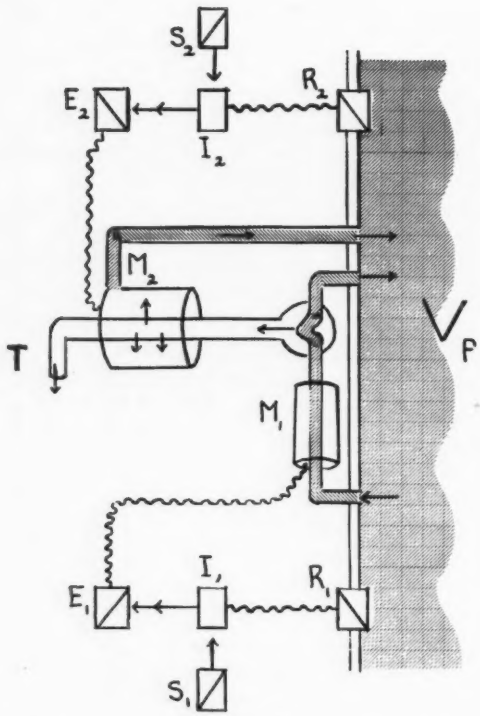

Figure 6

Scheme of the renal outflow as a complex tap regulated by servomechanisms, (compare fig. 4). The tap T, is represented as a single tube (nephron). Plasma from the plasma tank, V_p, shown on the right, is circulated at pressure by a servomotor, M_1, through the closed end of the tap in which a filtrate is formed. This represents glomerular filtration, and the rate is regulated by the system R_1, I_1, S_1, and E_1 acting on M_1, (compare fig. 4). Reabsorption from the tubule is pictured as controlled by a second servomotor, M_2, regulated by R_2, I_2, S_2, and E_2. Separate M_2 systems must exist for water and salt excretion.

are incompletely known, but some of our own experiments suggest that breakdown is relatively constant. Hence, it is possible that any existing regulation is of synthesis. Presumably the rate of synthesis of albumin will depend on the total number of albumin-synthesizing liver cells and the average number of albumin assembly lines in them. Thus, the rate of synthesis could depend on cellular growth factors and factors determining the size of the nucleic acid protein production lines. There is good evidence of the potentiality of the liver cells to multiply. For instance, after partial hepatectomy, when the total quantity of circulating plasma proteins starts to fall, the remaining liver cells increase their mitotic rate, the ribose nucleic acid content of the cells increases, and, in the rat at least, the bulk of the lost liver has been restored in a few weeks.[12] If a partial hepatectomy is performed on one rat of a parabiotic pair, an increased mitotic rate is seen in the liver cells of the other animal, suggesting that a hormonal growth factor is active.[13] But this essentially is as far as our knowledge goes; and, as with the red cell, we cannot say whether the total quantity of any, or all, of the plasma proteins is truly regulated in the defined sense of this word.

So far little convincing evidence has been found for regulation of the red cell or plasma volumes. But, to conclude, we note briefly 2 reflexes that appear to be regulatory, though their importance is at present uncertain. The walls of the right and left atria are supplied with a rich nerve network containing nerve terminals similar to those in the carotid sinus. According to Henry and collaborators[14] stretch of the left atrium, as by distention of an indwelling balloon, leads to production of afferent impulses that pass to the hypothalamus via the vagi and there inhibit the release of the antidiuretic hormone, so leading to a water diuresis. Farrell[15] suggested that stretch of the right atrial receptors evokes afferent impulses that lead to the inhibition of the release of another hormone from the diencephalon, which in turn regulates the secretion of aldosterone by the adrenal gland. This might result in some increased loss of sodium chloride from the body. These stretch receptors in the atria are in direct relation, through the atrial tension, with the volume of blood in the atria, and it has been suggested that this volume varies directly as the volume of blood in the great veins and low-pressure portion of the cardiovascular tree.[16] After integration in the central nervous system the error signal is transmitted by hormones acting on the kidney, that is on the outflow taps

of the water and salt flux systems. The controlling devices are pictured in servomechanism terms in figure 6. As shown, the kidney consists of a complex outflow tap. One servomotor, M_1, controls the rate of glomerular filtration, and the second, M_2, the rate of tubular reabsorption. The reflexes are both believed to act by hormones on the second servomotor, M_2. Though evidence indicates that the first effector, M_1, is of great importance,[17] we at present are almost entirely ignorant of its regulation.

Summario in Interlingua

Le question de si o non il existe un systema regulatori del volumine de sanguine es precisate per le autor in le forma del question de si o non il existe systemas de signales—de character nervose o hormonal—que responde a deviationes ab le nivello optimal del volumine de sanguine per activar mechanismos que servi a restaurar le volumine de sanguine a su nivello optimal.

In su analyse de iste question, le autor comencia per describer le factores de que le volumine de sanguine depende, tractante separatemente le mechanismos que provide (1) le volumine erythrocytic e (2) le volumine del plasma.

Le responsa al question initial consiste in le conclusion que il existe a iste tempore certe indicios que pote justificar le supposition del existentia de un systema de regulation hormonal del volumines erythrocytic e plasmatic sed que extense recercas additional va esser requirite pro transformar ille supposition in un facto demonstrate.

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Regulation of Water and Electrolytes

By J. Russell Elkinton, M.D.

TO INCLUDE a discussion of the regulation of total body water and electrolytes in such a symposium on the cardiovascular system at first glance may require some justification. It should be quickly apparent, however, that the total body fluids and the circulatory system are so intimately interrelated that consideration of one without the other would be quite incomplete. Part of the body fluids, the cellular fluids of erythrocytes and the plasma, are distributed within the vascular system and constitute the medium, so to speak, upon which the circulatory system operates. Being that which is circulated, these fluid phases are an integral part of the circulatory system. Likewise the circulatory system is essential to the integrity of the fluids of the body. The circulation provides the mixing apparatus that maintains the homogeneity of multiple and widely separated portions of the body fluids and the circulation is the link of the organs of exchange with the external environment. It would seem proper, therefore, to include water and electrolytes in this discussion of regulation of the cardiovascular system.

The concept of regulation as already defined by our moderator can be applied to the body fluids as well as to the rest of the cardiovascular system. In the consideration that follows, I shall attempt to show not only that physiologic servomechanisms are operative but that a great deal remains to be learned of their *modus operandi*. The emphasis will be on the holes in, rather than the substance of, our knowledge.

Evidence That the Total Body Fluids are Regulated

Let us begin simply by considering the 2 major dimensions of any fluid, including body fluids, namely, concentration and volume. It has been known for many years that the total concentration of solutes, or osmolality, of plasma and extracellular fluid is maintained within rather narrow and constant limits. This constancy of osmolality or tonicity was one of the features of the *milieu interieur* of Claude Bernard. It holds in amphibians, birds, and mammals and has been the subject of much investigation in the field of comparative physiology. On the other hand, constancy of volume of the body fluids has received relatively little attention until recent years. In 1916 that very shrewd observer of natural phenomena, L. J. Henderson, presented before the National Academy of Science a short note on the importance of volume in biology[1] in which he pointed out that at a given level of development the maintenance of a constant volume is one of the basic properties of living organisms. Evidence for this phenomenon in our own bodies is to be found in the constancy of our body weights. Since body water constitutes such a large proportion of body weight, rapid fluctuations in the latter must approximate changes in the former. This is true, of course, only if concomitant changes in body fat are not being induced by neurogenic or iatrogenic dietary manipulations, or by the more natural processes of growth or senescence. On one occasion I measured my own basal body weight daily for 56 days; the 2 standard deviation variations about the mean did not exceed ±1 per cent. This observation suggests that my total body water content was being regulated. In figure 1 are shown, again in myself, the oscillations in weight that occurred within one recent 24-hour period. On this Saturday away from the hospital, intake of food and fluid at breakfast was followed by considerable loss of body water and salt during the heavy exercise of cutting grass. At lunch a large thirst as well as hunger led to a copious intake; this was followed by a less

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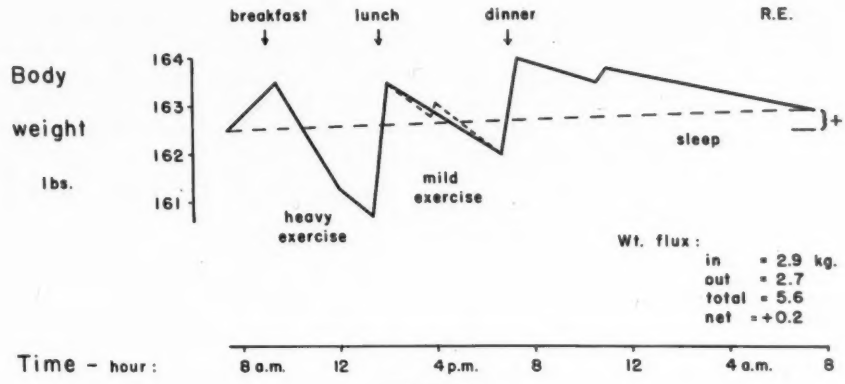

Figure 1

Oscillations of body weight during a 24-hour period.

rapid loss of body water during an expedition with my young son to the zoo. A mid-afternoon oscillation (dotted line) occurred due to ingestion of peanuts and root beer but was unmeasured. Intake at dinner was succeeded by a slower rate of loss during the evening and sleep. At the end of the 24-hour period my body weight had changed by only a plus 0.2 Kg. while the total weight flux was 5.6 Kg. (2.9 in, 2.7 out). These oscillations approximate the fluctuations of total body fluid and delineate very nicely the operation of intake and output servomechanisms that regulate diurnally the volume of my total body water.

These servomechanisms are the main subject of my contribution to this symposium. It is a subject of concern to the physician as well as to the physiologist and biologist. In disease, servomechanisms go wrong; the result is a sick patient requiring diagnosis and treatment. The primary pathogenic factor may be a lesion of the heart, the kidney, the adrenal cortex, the brain, or other organ; the result may be one or more disturbances in volume or osmolal concentration that we label congestive heart failure or edema, or dehydration, or hypernatremia or hyponatremia, and so on. But proper therapy needs an understanding of the servomechanisms involved in the patient's disturbed homeostasis. Let us as physicians consider these mechanisms of regulation.

Regulation of Water Relative to Solute

Osmolal regulation through the neurohypophyseal antidiuretic hormone (ADH) system is perhaps the best delineated servomechanism in the physiology of body fluid. The classic experiment in support of this mechanism was that of Verney,[2] who demonstrated that hypertonic solutions of sodium salts or sucrose, but not urea, infused into the arterial blood supply of the hypothalamus of the dog would inhibit a pre-established water diuresis to the same degree as a known amount of pitressin (fig. 2). From his observation Verney postulated that there must be receptor cells, sensitive to osmolal changes in the extracellular fluid bathing them, that control the rate of release of antidiuretic hormone (ADH) from the posterior pituitary. These sensitive loci he designated "osmoreceptors," and he presented evidence that they responded to changes in osmolal concentration of the order of 1 to 2 per cent.

It is now possible to characterize this servomechanism that regulates body water content relative to solute content (fig. 3). The stimulus on the afferent side of the arc is change in the total concentration in extracellular fluid or plasma of solutes that do not readily penetrate cells, (or, more precisely, change in the concentration of water). The effect of this stimulus on the receptor center is to alter the rate of release of an efferent humoral mediator,

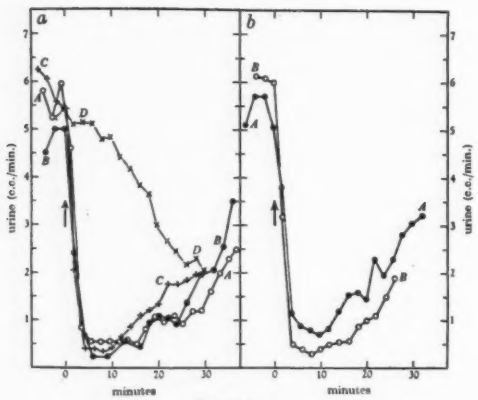

Figure 2

One of Verney's experiments demonstrating the antidiuretic effect of hypertonic solutions injected at different times into the carotid artery of a water-loaded dog. In graph a *are shown the effects of 2 ml. of 1.28 M NaCl (A), 0.98 M Na_2SO_4 (B), 2.39 M dextrose (C), and 2.39 M urea (D). In graph* b *are shown the effects of 2.5 (A) and 3.5 (B) mU of posterior pituitary extract. (From Verney, E. B.[2] Reproduced by permission of the publisher and the author.)*

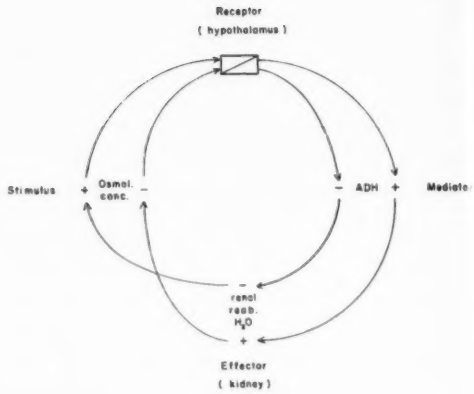

Figure 3

Regulation of osmolal concentration by water output.

antidiuretic hormone. This hormone, ADH, produces in the effector organ, the kidney, a change in rate of tubular reabsorption of water, and hence the rate of water output. The result is a modification of the original osmolal stimulus—in cybernetic terms, correction of an error by negative feedback.

It must here be pointed out that a variety of other stimuli act on the neurohypophyseal system to produce changes in the rate of release of ADH.[3] These stimuli, listed in table 1, strongly suggest that the hypothalamic center is subject to signals from areas of the central nervous system above the diencephalon. The experimental observation that changes in volume somewhere in the intravascular portion of the extracellular fluid also affect ADH release, is important and is discussed below.

So far we have discussed a servomechanism that regulates water content relative to solute only by regulation of water output, i.e., through adjustment of overflow through the kidney. The kidney, however, can never make up a deficit; equally important and essential to the maintenance of a steady state is the regulation of water intake. Although thirst, the effector system that leads to drinking, is a complex physiologic mechanism, there is no doubt that one of the principal stimuli is a rise in osmolal concentration. The receptor center for this stimulus again is in the hypothalamus adjacent to and, indeed, overlapping the area containing the osmoreceptors controlling ADH release. Figure 4 indicates that water regulation involves dual integrated servomechanisms operating on both intake and output of water. As in the case of ADH release, stimuli other than extracellular osmolal concentration stimulate thirst; these include habit patterns, conditioned reflexes, oral sensations, and changes in volume of extracellular fluid and perhaps of intracellular fluid as well.[4]

This dual mechanism for the regulation of body water relative to solute, however, is only part of the story. Unless the latter also be regulated, the body might swell to the point of bursting or shrink to the point of near-desiccation according to the fortuitous vagaries of solute content, the osmolal concentrations being maintained withal within constant limits. Regulation of solute content, therefore, is primary to regulation of the water or osmolal concentration if the volume of body fluids is to remain constant.

Table 1

Osmolal Regulation. Factors Affecting the Rate of Release of Antidiuretic Hormone

Stimulation: - ADH release - Inhibition:	
H_2O reabsorption ↑	H_2O reabsorption ↓
H_2O excretion ↓)	(H_2O excretion ↑)
↑ Osmolal concentration in extracellular fluid ↓	
↓ Volume: extracellular and intravascular fluid ↑	
Emotion	Alcohol
Exercise	Inhalation CO_2
Sleep	
Anesthesia	
Nicotine	

Regulation of Solute Content, and Hence of Volume

The servomechanisms subserving this body fluid parameter are much less clearly understood than are those involved in osmolal concentration. And yet the reason for suspecting their existence is compelling, namely, the constancy of body weight to which I alluded at the start of this presentation. What is known of this servomechanism?

John P. Peters in 1935[5] pointed out that the excretion of sodium, the principal extracellular electrolyte, must somehow be responsive to changes in volume of the extracellular fluid, most probably to some intravascular portion of that fluid phase. Subsequently Borst[6] in 1948 suggested that the renal secretion of sodium is related to cardiac output. Since then a host of investigators have provided evidence that changes in intravascular fluid volume and hemodynamics induced in the head, the thorax, the abdominal cavity, or the extremities will lead to changes in rate of excretion of sodium and water; some of these factors as experimentally demonstrated are listed in table 2 (modified from Robinson[7]). Although it is apparent that considerable uncertainty obtains in both the afferent and efferent portions of this regulatory circuit, it is possible to construct a tentative schema to outline the servomechanisms that must be involved, (fig. 5). The stimulus must be a change in volume at one or more loci in the circulatory system. Changes in pressure in the left atrium have been shown to lead to changes in the rate

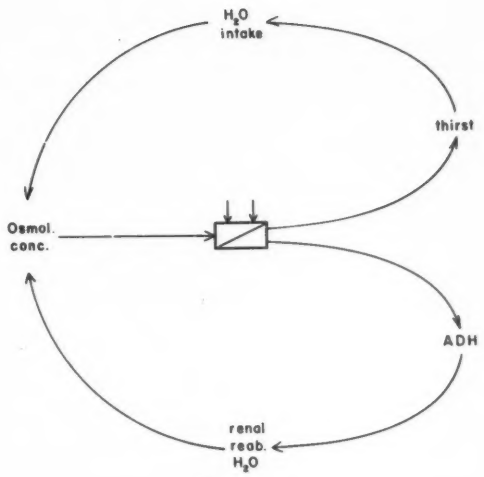

Figure 4

Regulation of osmolal concentration by water intake and output.

of water excretion.[8] This reflex appears to be dependent on continuous pulsatile stretch of the atrial wall[9] and the afferent nerve fibers are carried in the vagus.[10] In contrast, changes in excretion rate of sodium rather than of water are produced by alterations in pressure in, and stretch of, the right atrium and great veins, apparently through the mediation of aldosterone.[11] In view of the variety of conditions that lead to changes in sodium excretion it is most probable that the degrees of filling of the vascular tree in both the venous and the arterial sides are stimuli in multiple receptor sites. From these receptor sites afferent neural pathways must lead to an integrating center in the central nervous system, again location unknown.

The efferent arc has been the subject of considerable recent investigative activity; the effector organ is the kidney but is the mediator humoral or neural or both? Changes in rate of aldosterone secretion have been shown to be affected by experimental alterations in extracellular fluid, and especially in plasma volume.[12] Cross-circulation experiments to normal dogs from dogs with constricted inferior venae cavae (an experimental preparation known to lead to increased secretion of al-

Table 2

Volume Regulation. Factors Affecting the Rate of Sodium Excretion

Stimulation:	Inhibition:
Na reabsorption ↑	Na reabsorption ↓
(Na excretion ↓)	(Na excretion ↑)
↓ Volume: extracellular and intravascular fluid ↑	
Experimental	
Hemorrhage, shock	Intravenous hypotonic saline in water loaded subject
Upright posture	Intravenous isotonic saline
Cuff on proximal portion of limbs	Supine posture
Abdominal compression	Compression neck
Balloon in inferior vena cava	Lowering central venous pressure in congestive heart failure with digitoxin
Constriction inferior vena cava	
Intravenous hyperoncotic albumin solution	Compression of legs by elastic bandages

dosterone[11]) have demonstrated that the trigger to increased aldosterone production in the second dog is a humoral agent.[13] It is not ACTH and, as far as I know, it has not been identified biochemically. Hence in figure 6 it is labeled *X hormone,* although some workers have called it *glomerulotropin.*[11] These experiments, of course, suggest that 2 humoral mediators (one from the adrenal cortex) are involved in the efferent arc of this regulatory circuit. On the other hand, there are some further observations that cast doubt on the role of an adrenocortical steroid as the sole efferent mediator. Some of the experimental manipulations of fluid volumes, such as production of intracranial congestion or rapid infusion of hypotonic saline solutions, have been shown to be equally natriuretic in patients or animals with diseased or absent adrenal glands.[14] Such observations have led to the postulation by Dr. Homer Smith of an antinatriuretic hormone ("ANH") that perhaps is elaborated in the neurohypophysis and acts directly on the renal tubule.[15] These findings also have raised again the possibility of a direct neural efferent pathway to the kidney. Only 2 experimental studies in support of such neural pathway will be cited. One is the finding that a completely denervated kidney, as transplanted from an identical twin donor, does not respond in a normal way to some of the experimental volume manipulations listed in table 2.[16] The other is the demonstration in the dog with experimental congestive heart failure that injection into one renal artery of an epinephrine-norepinephrine antagonist will lead to unilateral changes in sodium excretion by that kidney, thereby suggesting interference with the action of an abnormal sympathetic tone.[17] In view of the variety, if not the contradictory nature, of a plethora of experimental evidence, we must conclude that much remains to be learned of the servomechanisms involved in the regulation of sodium content and volume of extracellular fluid.

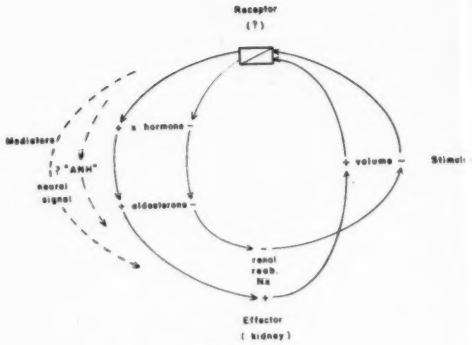

Figure 5

Regulation of sodium content and extracellular fluid volume by sodium output.

Integration of Volume and Osmolal Regulation

Nevertheless, from what has been presented we may feel sure of the existence of servomechanisms for regulation of these functions or dimensions of the body fluids. That the primary mechanism for regulation of sodium content and volume of extracellular fluid must be closely coordinated with the secondary mechanism of osmolal concentration, or water relative to solute, hardly needs to be said. In figure 6 the relationship is presented schematically of these double regulatory circuits. On the left is shown that which concerns sodium content and fluid volume; a possible but undemonstrated circuit involving

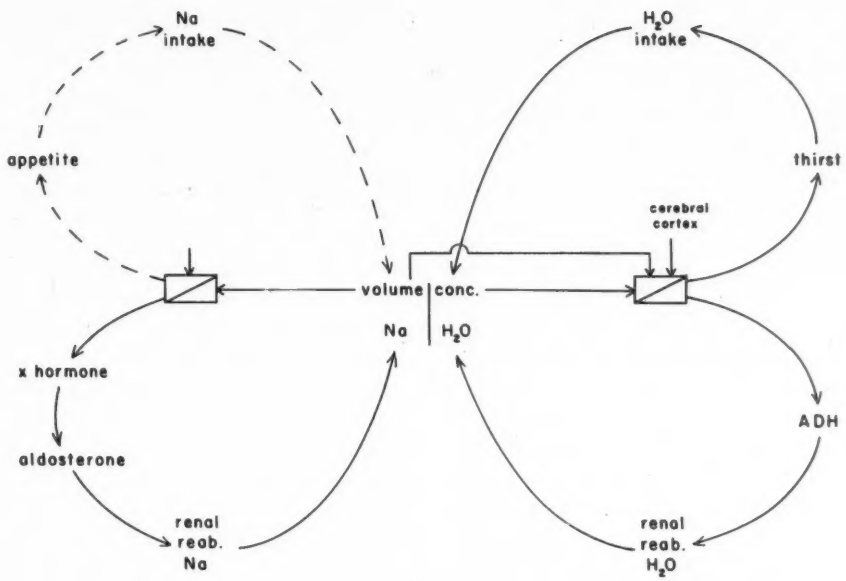

Figure 6

Relation of volume regulation to osmolal regulation.

appetite and sodium intake is indicated by a broken line. Nothing has been said previously about a servomechanism for regulating intake of sodium because essentially little is known about such a mechanism; the kidney may operate only on overflow of an entirely fortuitous intake of this solute. In any case, the output regulatory circuit operates through the kidney as effector organ with an efferent mediator that is either neural or humoral (as shown) or both. The secondary regulation of the amount of water relative to the amount of solute, or osmolal concentration, is presented on the right in figure 6. The principal stimulus, change in osmolal concentration, acting on a single or on several closely integrated hypothalamic receptor centers, effects a change in water intake through thirst and in water output by mediation of the antidiuretic hormone acting on the kidney. In addition, the receptors in these 2 circuits are directly stimulated by changes in volume of some portion of the extracellular fluid;[3, 4, 18, 19] other stimuli from higher levels in the central nervous system must play only an occasional and intermittent role in this regulation. This schema as presented is deceptively oversimplified but represents in broad outline the general plan and relationships of these 2 dual integrated servomechanisms that are responsible for the regulation of water and solute content of the extracellular fluid of the body.

Some of the Things That We Do Not Know

These are many, and their appraisal is conducive to humility. Such appraisal perhaps is best conducted within the frame of reference of the concepts of cybernetics or information theory as outlined by our moderator in his introduction to this symposium.

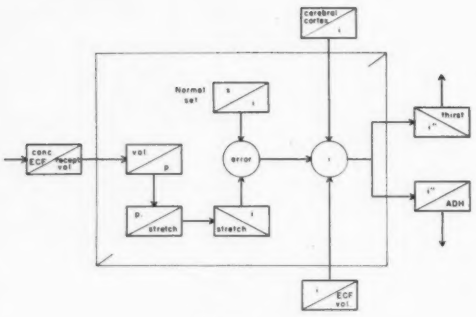

Figure 7

Possible transfer functions of the osmoreceptor.

Let us first consider the mechanism of *osmolal regulation,* since of the 2 servomechanisms that we have been discussing this is the more clearly delineated. Is the hypothalamic osmoreceptor one cell or a large number of cells in an area? Is the response to an osmolal stimulus a graded response per cell or is it an all-or-none response that produces a graded total efferent signal according to the number of cells responding? Does the stimulus act on synapses or on neurones? What are the transfer functions in the osmoreceptor? A possible schema for such is shown in figure 7. Here it is suggested that a change in extracellular osmolal concentration produces (via an osmotic shift of water) a change in receptor cell volume; the volume change at least transiently alters pressure, which in turn results in stretch of the cellular membrane. The stretch is then converted into an information signal, presumably electrical in nature. This sequence, of course, is almost entirely speculative, for there is very little direct experimental evidence in its support; it is quite possible that the change in osmolal concentration produces a signal in some other way. Some of my colleagues, however, have established that neurones growing in tissue culture undergo changes in volume when the osmolal concentration of the surrounding medium is altered; currently they are investigating the possibility that differential volume changes between dendrites and axon hillock may lead to alterations in electrical potential of the cell.[20] Almost everything remains to be learned of the conversion of a change in osmolal concentration into a signal of information.

And given such an information signal, it must then be compared, if a self-correcting servomechanism is operative, with an ideal or "normal set" value in order to quantitate the error that needs to be corrected. In the case of body fluid osmolal concentration the normal set value is a phylogenetic inheritance that is much the same throughout most vertebrate species. How it functions in the osmoreceptor is quite unknown. If change in volume due to osmotic shift of water is the critical transfer function, then the normal value must be set by the amount of osmotically active solute present inside the receptor cell. Some years ago we hypothesized that an alteration in this factor must be responsible for the abnormal set of the osmoreceptor-ADH system in certain patients with persistent hyponatremia or hypo-osmolality of their body fluids.[21] But we are totally ignorant of the factors in health or disease that condition the quantity of osmotically active intracellular solute in these particular receptor cells.

In any case, the error having been measured, an efferent information symbol (i' in figure 7) must then be further integrated with the signals from other efferent stimuli from volume receptors and from the cerebral cortex. The resultant modified information (i'' is then sent out on the efferent arcs of both the intake and output-regulating circuits. No attempt is made to list here the many questions concerning the efferent mechanism of thirst or concerning the mode of action of the antidiuretic hormone in the renal tubule.

Turning to the regulatory system for *extracellular solute content and hence for volume* we find an even greater number of unanswered questions. The uncertainties about the precise stimuli and the sites of reception of those stimuli have already been set forth. The transfer functions of such volume receptors are also a matter of conjecture. There is more direct experimental evidence than in the case of osmolal regulation to support a volume —→

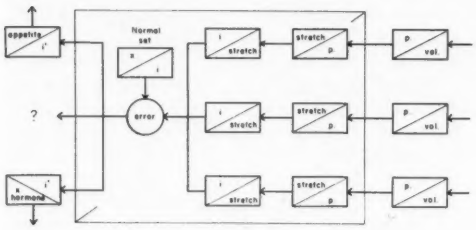

Figure 8

Possible transfer functions and integration of volume receptors.

pressure ⟶ stretch sequence fig. 8 in the volume receptors in the right atrium,[11] the left atrium,[8] and in other loci in the arterial system.[7, 22] Wherever and however initiated, information signals must be integrated with each other somewhere in the central nervous system, presumably the hypothalamus. Again that information must be compared with an ideal or normal set value in order to measure the error to be corrected (fig. 8). Of the mechanism for maintaining the normal "set" and making this comparison, I have not the faintest clue. But the error is determined and the resultant modified information is then sent out over an efferent arc of which we have only fragmentary knowledge of a humoral portion. Truly, we have much to learn.

There are ancillary areas of ignorance that should at least be mentioned. Throughout this discussion we have stressed the control of circulating hormone levels solely in terms of production of the humoral mediating agents. The rate of destruction of humoral agents also may be an important factor in regulation. At any given moment the amount of hormone present in the circulating blood stream is a function of both the rate of production and the simultaneous role of destruction. This concept complicates our inquiry and extends our uncertainties. Another puzzle that is related to our subject is the role of electrolytes, and especially of sodium, in the wall of arterial blood vessels. To what extent, and how, is arterial wall sodium related to the complicated regulations of total peripheral resistance and peripheral blood flow that have been detailed by previous speakers? These, too, are questions awaiting answers.

Table 3

Homeostatic Goals in Maintaining the Integrity of the Organism

	Extracellular		
Plasma Volume ↓ Integrity of Circulation ↓ Exchanges with Environment	← Volume Na	Conc. → H_2O	Intracellular Volume ↓ Integrity of Cellular function

Conclusion

Regulation implies an ideal function or a homeostatic goal, as it were, on the part of the organism. This is not teleology but biologic fact, although Drabkin[23] has pointed out how very imperfect most homeostatic mechanisms are. If we define the homeostatic goals of the organism in terms of maintenance of its integrity, we can attempt to fit the regulations that I have been discussing into the general homeostatic scheme (table 3). Regulation of extracellular solute content and volume supports the plasma volume, and this in turn is essential to the integrity of the circulation. On the circulation depends all the multifarious exchanges between the organism and the external environment. Regulation of water relative to extracellular solute, or osmolal concentration, on the other hand, directly affects the volume of fluid inside cells by means of the osmotic shift of water. The other factor that conditions the volume of intracellular fluid is the amount of osmotically active solute present inside the cells; but the regulation of this factor lies outside the purview of our symposium. In any case, regulation of cell volume must be essential to proper cellular function. So the 2 servomechanisms that we have been discussing contribute to the integrity of the organism by subserving both its cellular function and its exchanges with the external environment—an ample excuse for their inclusion in the present discussion.

Summario in Interlingua

Regulation presuppone un function ideal, un objectivo homeostatic (a si dicer) del parte del organismo. Isto non es teleologia sed facto biologic,

ben que Drabkin ha signalate le extreme imperfection del majoritate del mechanismos homeostatic. Si nos defini le objectivos homeostatic del organismo ab le puncto de vista del mantenentia de su integritate, nos pote interprender le tentativa de visualisar le hic-discutite typos de regulation—illo del aqua e illo del electrolytos—in un schema de homeostase general. Le regulation del contento extracellular de soluto e del volumine del liquido extracellular supporta le volumine del plasma, e isto—de su parte—es essential pro le integritate del circulation. Omne le multiple formas de excambio inter le organismo e le ambiente externe depende del circulation. Del altere latere, le regulation de aqua in relation al solutos extracellular, o le concentration osmolal, affice directemente le volumine de liquido intra le cellulas per le agentia del transition osmotic de aqua. Le altere factor que conditiona le volumine de liquido intracellular es le quantitate del osmoticamente active soluto que es presente intra le cellulas (sed le regulation de iste factor non es parte del thema formulate pro le presente symposio). In omne caso, le regulation del volumine cellular debe esser essential al normal function cellular. Assi le duo servomechanismos discutite in le presente analyse contribue al integritate del organismo per le facto que illos es subserviente al function cellular e al excambio del organismo con le ambiente externe, e isto es plus que adequate como justification de includer los in le presente symposio.

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CLINICAL CONFERENCE

Clinical Management of Atherosclerosis

Edited by E. SILBER, M.D., R. PICK, M.D., AND L. N. KATZ, M.D.

DR. LOUIS N. KATZ: This meeting is not intended as a conference on the pathogenesis of atherosclerosis. Those of us engaged full time in such research have ample opportunity for the exchange of ideas and the airing of opinions at numerous meetings where the results of investigation are presented. More important at the moment, I think, is the need for a conference the purpose of which is to extricate the clinician from the avalanche of conflicting, heterogeneous, new information relating to atherosclerosis. The busy physician in practice is bombarded, on the one hand, by the medical and drug literature relating to fats and cholesterol; on the other hand, he is confronted by his patients who have picked up uncritical reports of new discoveries in diagnosis and treatment through the press, radio, television, and the lay magazines and expect the doctor to apply this so-called knowledge immediately to themselves. Are we surprised, then, that the physician is struggling to maintain his equanimity, and to differentiate that which is established and clinically useful from that which is speculative or clinically inapplicable. I cannot resist the temptation, as an irrelevant aside, to point out that it is just for such reasons that I have always insisted that the "pure clinician" should have training in, or at least exposure to, the discipline of research methodology.

From this preamble it is obvious that the purpose of this conference is 3-fold: (1) to impart to the clinician those facts regarding the pathogenesis of atherosclerosis which are established and which have important clinical implications; (2) to suggest a specific prophylactic program which is warranted by the above facts; and (3) to outline a therapeutic program for the person with clinically evident atherosclerosis or its sequelae. However, myocardial infarction and angina pectoris will not be discussed as such.

I am aware that this is no mean task and that extraordinary efforts are required to succeed. Nor is it easy for the laboratory investigator to acquire or, once acquired, to retain the "clinical touch." To this end I have circularized those members of the medical staff of the hospital who are dealing with the problems of atherosclerosis for questions. I have taken their questions and apportioned them among the research and clinical associates of my own department. The specific questions assigned to each of them reflect his particular qualification by virtue of personal research activity or extensive clinical experience. I have not bullied a particular point of view from them, although I reserve the right to disagree as vehemently as it appears to me that the opinion they express warrants. In meditating over the same questions that I have parceled out to my associates, I was aware that in thinking clinically, my answers, at times, have a different nuance from viewpoints I have expressed in publications dealing with the pathogenesis of atherosclerosis in experimental animals. This is not surprising. There is neither chagrin nor apology on my part for this, for it merely points out the difficulty inherent in transferring, in toto, the data of animals to human disease and to its treatment.

We panelists have agreed to entertain addi-

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tional questions from the audience, or from one panelist to another, at any time during the discussion. At the very least I can promise this audience an unrehearsed, spirited discussion. To what extent we generate light rather than heat will be determined ultimately by the judgment of the clinician.

Now, because I have spoken a great deal more than I had intended, I am going to decline the privilege accorded me by my staff of opening the discussion. Instead, I will ask Dr. Ruth Pick, Assistant Director, and a principal figure in the department's atherosclerosis research program to deal with the question: Is it quite clear that the development of atherosclerosis is related to the ingestion of fat?

DR. RUTH PICK: It is certainly of some historical as well as practical interest to point out that the very phrasing of this question indicates awareness that dietary cholesterol is not the only important factor influencing the level of serum cholesterol, and, therefore, is presumably not the sole determinant in the development of human atherosclerosis. The protein, mineral, and vitamin content of the diet is also of importance provided the diet has enough fat and cholesterol to be potentially atherogenic. Dietary fat also has a significant influence on serum cholesterol levels. Animal experimental studies have shown that the atherogenicity of a cholesterol-containing diet rises as neutral fats—saturated or unsaturated—are added in increasing amounts. Upon withdrawal of this diet, atherosclerosis undergoes gradual regression.

From an epidemiologic point of view it has been demonstrated by a number of investigators that the environmental factor that correlates best with coronary disease is total fat consumption—particularly that of animal fat. In all countries where fat intake is high, the incidence of atherosclerosis is high as judged both by the findings of gross pathology and from the morbidity and mortality statistics of heart disease. These findings emphasize that ethnic and racial factors are not the primary determinants of international patterns of coronary heart disease. A step-wise increase in coronary mortality is seen with an increase of fat intake up to 120 Gm. daily when a large proportion is derived from animal sources. Above this level coronary mortality is high, but variable, and does not parallel the intake of fat. Conversely, in Central Europe during the famine following World War I, and in Scandinavian and Low Countries and during the siege of Leningrad in World War II, a marked reduction in intake of total fats, and animal fats, was associated with a decline in mortality rates from arteriosclerotic heart disease.

However, a disparity in dietary fat intake is not responsible for the striking difference in the coronary disease morbidity and mortality of American men versus women, of urban versus rural man in the northern United States, of British consultants versus general practitioners, or, finally, of English bus drivers versus conductors. These discrepancies serve to emphasize that the relationship between diet and atherosclerosis is not 1-to-1, and that while diet is a major factor, multiple factors interact to influence the emergence of clinical coronary disease. A number of these factors will be the subject of subsequent discussions by other panelists.

DR. KATZ: I would go one step further than Dr. Pick by stating, parenthetically, that I believe the epidemiologic evidence relating the development of atherosclerosis to dietary fat is good enough to warrant advocating a conservative revision in the American diet, especially for the individual with a high risk of developing coronary heart disease. The alteration I have in mind is simply a reduction of fat intake from the present 40 to 60 per cent of total calories down to 20 to 30 per cent, with an approximate 3 to 1 ratio of vegetable to animal fat. Of course, the vegetable fats should be fresh and nonhydrogenated.

PHYSICIAN: How do you explain the anatomic variation in atherosclerosis if the disease is a manifestation of disturbed fat metabolism?

DR. KATZ: Since Dr. Pick is our experimental pathologist, I will assume the question is directed to her.

DR. RUTH PICK: There is no complete explanation at the present time for the predilection of one portion of the circulation to be the site of atherosclerosis as compared to another. A number of facts suggest that mechanical factors are involved. In the first place, atherosclerosis develops in large and medium-sized arteries, rarely in the smaller vessels. Secondly, atherosclerosis is not found in veins. Atherosclerosis is found in the pulmonary arteries only in the presence of hypertension of the lesser circulation. Finally, lesions develop mainly at bifurcations and flexions where the stream strikes directly against the vessel walls. It would appear, then, that atherosclerosis occurs in vessels that receive most of the impact of ventricular systole, in vessels that are loosely supported and less restricted in movement, at sites of increased turbulence, eddy currents, and jets, and in such conditions as hypertension, in which the pulse pressure is high. In short, lesions abound wherever and in whatever circumstances pulse movements are accentuated. The demonstration of the operation of mechanical factors does not preclude the possibility of a genetic influence determining the site of atheroma formation. However, little direct evidence in this regard is available at present.

DR. KATZ: Dr. Pick has dealt with these 2 complex aspects of the problem with remarkable clarity and lack of equivocation. I have assumed the prerogative of directing myself to the next question because it is one that is invariably put to me in addressing professional groups around the country. It is always open season for needling us about our preoccupation with the rooster. The question relates to whether atherosclerosis of man is closely related to experimentally induced atherosclerosis in animals.

The answer, in my opinion, is yes. In all species of experimental animals, whether it be the chicken, monkey, rabbit, dog, or rat, atherosclerosis can be produced only by disturbing lipid metabolism. While these observations cannot be transferred to human subjects literally, that they are cogent is suggested by convincing evidence of the association of hypercholesteremia with human coronary heart disease, and the occurrence of severe, premature atherosclerosis in disease states characterized by hypercholesteremia and hyperlipemia. It is true that histologically the lesions in animals while similar are not identical to those in man, but the same can be said for the chancre in rabbits that are the subjects of experimentally induced syphilis.

Much of the difference in the atheromata, I think, is a matter of the age of the lesions. In the laboratory it is not expedient to carry on experiments until "full-blown" lesions have evolved—we are far too impatient. For this reason we seldom see calcification or fibrosis, but these stages occur when animals are maintained on the atherogenic regimen long enough. Recently, we have produced ulcerated lesions in chickens, and coronary thrombosis in rats has been reported by others. Admittedly, the counterpart of clinical syndromes such as strokes, myocardial infarction, aneurysm, or peripheral vascular disease is rarely observed in experimental animals. However, these animals rarely grow old in the laboratory, and examinations of the cerebral circulation in chickens and other test species have not been carried out to any great extent because of the enormous technical difficulties involved. Occasionally, aneurysmal dilatation of the aorta and dissecting aortic aneurysm have been noted in the chicken, and, as previously mentioned, coronary thrombosis has been described in the rat.

There is no question that important clues to the pathogenesis and therapy of atherosclerosis in man have been gained from animal experiments—studies that could not have been carried out in man. Ultimately, however, the answer must be sought in man himself by testing the facts of animal studies on him.

It is to be expected that there is intense interest in the usefulness of the various "blood tests" to indicate either the presence of significant atherosclerosis or the abnormal tendency to develop such lesions. I shall ask Dr. Harold Feinberg, our biochemist, to comment on this important facet.

DR. HAROLD FEINBERG: These tests include

determination of total serum cholesterol, the ratio of serum cholesterol to phospholipids, levels of alpha and beta lipoproteins, and estimation of the classes of low-density lipoproteins separated by ultracentrifugation. From a practical standpoint, the total serum cholesterol provides the information necessary to indicate whether there is an increased tendency to develop atherosclerosis. There is no question that coronary artery disease is more prevalent in individuals with an elevated serum cholesterol. Many of the subjects with infarcts are found above the midpoint, between the 50 to 75 percentile of the serum cholesterol distribution curve. A serum cholesterol below 180 mg. per cent can be regarded as "nonatherogenic," a level above 250 mg. per cent, as constituting "high-risk." Cholesterol levels between these 2 limits are intermediate insofar as the occurrence of clinical coronary artery disease is concerned. In men under 35, a low serum alpha-lipoprotein is valuable in detecting a high-risk group. Estimation of the beta-lipoprotein fraction has been of no special value either from the diagnostic, prognostic, or therapeutic point of view. This is not meant to imply that study of the serum lipoproteins will not continue to be a valuable research tool.

PHYSICIAN: Would you comment specifically on what has been termed the "atherogenic index?"

DR. KATZ: It was my impression that Dr. Feinberg's remarks made it clear that the determination of the serum total cholesterol is the most important single blood test in relation to atherosclerosis. At the risk of being repetitious, may I emphasize that the determination of various lipoprotein fractions of the serum has no advantage insofar as diagnosis is concerned, despite the continuing value of the technic in research studies.

We are reaching a point in this conference where we can concern ourselves with the practical matter of the treatment of clinical atherosclerosis. Dr. Langendorf, how would you treat patients with increased concentration of lipids in the blood?

DR. RICHARD LANGENDORF: When you say "increased concentration of lipids in the blood," I think you and your research associates will bear me out in stating that there is no clear-cut relationship to atherosclerosis of hyperlipemia unaccompanied by hypercholesteremia. The role of simple hyperlipemia with respect to blood clotting remains to be elucidated. However, it is somewhat arbitrary to make a simple distinction between hyperlipemia and hypercholesteremia because, with the passage of time, the former "leads to" the latter. Patients with simple hyperlipemia usually respond very well to a low-fat diet. It is of interest that their serum is cleared easiest by heparin.

DR. KATZ: Such treatment, however, is one that, at present, requires further careful evaluation before it can be applied on any extensive clinical scale.

DR. LANGENDORF: The risk of coronary heart disease is greatly increased in the patient with hypercholesteremia. To date no data are yet available to show that lowering the blood cholesterol changes the incidence of atherosclerosis in human beings. It is obviously a moot question whether lowering the serum cholesterol from 400 to 270 mg. per cent constitutes any real therapy, since the latter level itself is atherogenic, although presumably less so. Therapeutic efforts to lower serum cholesterol rests upon epidemiologic and experimental evidence that hypercholesteremia leads to atherosclerosis and lowering serum cholesterol leads to regression of lesions in animals. There is widespread agreement among experts in the field that attempts, with reasonable dietary correction, to lower serum cholesterol in the hypercholesteremic individual are warranted by the facts that constitute our present knowledge. However, the optimal blood cholesterol level to ensure freedom from atherosclerosis still needs to be determined.

The general objective should be to correct obesity if it is present. Ideally, such patients should be reduced to a level below their ideal weight. These patients should be maintained on a diet in which the fat intake constitutes 20 to 30 per cent of the total calories. The whole matter of unsaturated fats as part of

the fat intake I shall leave to another discusser. If a low-fat diet alone does not bring the serum cholesterol level down low enough, I would add sitosterols to the therapeutic regimen. In sufficient quantities, taken before each meal, sitosterols will impair cholesterol absorption and lead to a lowering of serum cholesterol. Unfortunately, from a practical standpiont, the large quantities that are necessary to achieve this effect are unpalatable and quite costly.

PHYSICIAN: Dr. Langendorf, do you believe that patients who have coronary heart diseases, or other complications of atherosclerosis, should follow a diet sharply restricted in fat intake even if they have a normal concentration of lipids in the blood?

DR. LANGENDORF: In such patients attention should first be given to weight reduction in those who are over weight. Such weight reduction necessarily entails a reduction in fat intake. No single food need be eliminated from the diet, but the total calories derived from fat should not exceed 30 per cent. This would simply entail a reduction of the visible saturated fats, e.g., trimming meat, and consuming less high-fat dairy products. Each of us who sees any number of coronary patients has encountered those who experience angina pectoris after a heavy meal. It would, therefore, seem desirable to avoid heavy meals, particularly in the evening, to minimize the chances of intravascular clotting. This is probably especially true of heavy, high-fat meals. It has been demonstrated that reductions in serum cholesterol that are achieved by low-fat diets persist as long as the diet is maintained. Prolonged low-fat diets are not harmful. British children during World War II were healthier on a low-fat than on their unrestricted pre-war diet.

MEDICAL RESIDENT: Are the lipotropic agents or nicotinic acid valuable adjuncts to dietary treatment?

DR. KATZ: Dr. Miller, would you comment on these agents?

DR. ALBERT J. MILLER: Lipotropic factors such as choline, lecithin, and inositol, under certain experimental conditions appear to be limiting factors in fat transport but there is no evidence that they have a role in the prevention or treatment of atherosclerosis when there is no deficiency of them. Negative results have been obtained in most studies in man as well as in experimental animals. With few exceptions no hypocholesteremic effects have been observed. No data have been published on long-term prophylatic or therapeutic results.

Nicotinic acid in large doses (4 to 6 Gm.) results in significant lowering of the serum cholesterol in man. The mechanism of this hypocholesteremia is not known, nor has it yet been demonstrated that it is anti-atherogenic clinically. The unpleasant side effects of the high doses required seriously limit its usefulness as an adjuvant to diet therapy.

DR. KATZ: Dr. Pick, Dr. Langendorf alluded to saturated fats in his discussion of low-fat diets in the treatment of atherosclerosis. Would you review the current status of this subject?

DR. RUTH PICK: In 1952, Kinsell and his associates reported that whereas diets high in animal fats raised the levels of serum cholesterol and phospholipid in human subjects, diets equally high in vegetable fats decreased serum cholesterol and phospholipid. Within the past 2 years, it has been shown that mixed vegetarian diets, devoid of animal or other saturated fats, are also hypocholesteremic in their effect. These results are consistent with the finding that strict vegetarians have lower serum cholesterol levels than nonvegetarians or partial vegetarians who eat eggs or dairy products. A number of reports have established that isocaloric exchanges of different fats in the diet alter the serum lipids in proportion to the degree of unsaturation of the fat, and not apparently as a result of the animal or vegetable origin of the fat. In apparent contradiction to these results in man, experimental atherosclerosis has been produced for decades in rabbits and chicks by diets containing cholesterol and unsaturated vegetable oils. Moreover, in the absence of dietary cholesterol, diets high in unsaturated vegetable oils induced hypercholesteremia and atherosclerosis

in rabbits and squirrels. Recent experiments have further demonstrated that chicks fed mash high in cholesterol supplemented with either saturated or unsaturated oils exhibited little or no difference in hypercholesteremia and atherogenesis. Since the design of these animal experiments was not analogous to the human investigations, it would appear premature to attribute the contradictory findings to "species differences."

To return to data in human beings, the mechanism by which unsaturated fats lower the serum cholesterol is still not clear. That this lowering might be of great importance in preventing or retarding atherosclerosis is enhanced by the observation that linolenic acid will inhibit the intracellular deposition of lipid induced by cholesterol in tissue cultures of human aortic cells. Kinsell has reported "encouraging" results in patients with partially occlusive peripheral vascular disease maintained on diets relatively rich in polyunsaturated fats. Several years must elapse, however, before anything but the most tentative sort of conclusion can be drawn.

PHYSICIAN: Dr. Langendorf, in view of what Dr. Pick has just jointed out with respect to unsaturated fats, would you recommend their use in the treatment of patients who have clinical evidence of atherosclerosis?

DR. LANGENDORF: The answer is yes, but I should emphasize a number of important details. Unsaturated fats have little effect when taken in addition to the usual amount of saturated fat present in normal American foods. "Supplementation" diets, therefore, are doomed to failure. Reduction of saturated fats has the greatest effect on lowering serum cholesterol, and this effect may be enhanced by substitution of unsaturated fats. Accordingly, a diet in which 20 to 30 per cent of the total calories is derived from fat with a ratio of unsaturated to saturated fat of 3:1 or 4:1 is suggested for the patient with clinical atherosclerosis. Patients on such a diet should have its efficacy checked by periodic determinations of the serum cholesterol, since the ingestion of unsaturated fatty acids it not uniformly effective in lowering serum lipids. This is achieved in only 65 to 75 per cent of subjects. There is no change in the remainder, and an occasional patient may show a rise in cholesterol level.

Finally, it may be argued that dietary management of atherosclerosis following a stroke or myocardial infarct can do little more than arrest an already advanced process. One can point to the regression of lesions induced in animals by an atherogenic diet on removing the dietary cause, but this is not necessarily analogous to the situation in man. However, some indirect evidence for regression of human coronary atherosclerosis can be cited. Regression of such lesions would explain the low incidence of severe atherosclerosis in emaciated cancer patients. Regression of cutaneous xanthomata on a low-fat diet has been observed repeatedly. It is not unreasonable, therefore, to recommend a low-fat diet for the person known to be afflicted with atherosclerosis.

DR. KATZ: Before leaving the subject of diet and fats, I should like to ask Dr. Shaffer to comment on this question: Is it clear that obesity is associated with an increased incidence of coronary heart disease? Is there any evidence that weight reduction prevents coronary heart disease or helps patients who already have it?

DR. AARON B. SHAFFER: The widespread impression that obesity is a major factor in the development of coronary heart disease and that reducing confers protection is derived almost entirely from actuarial data of life insurance companies. Their experience demonstrates an apparently excessive mortality from cardiovascular disease among overweight policy holders. Doubts as to the validity of this conclusion have been raised by the detailed analysis of their data by Keys. More recently the Framingham study has indicated that obesity, as an individual defect, doubles the risk of coronary heart disease in men aged 45 to 62. Some contrary evidence exists. A long-term follow-up study of some 22,000 U. S. Army officers did not reveal a relationship between overweight and the occurrence of coronary heart disease. Yater and

his colleagues found that obesity was not a significant finding in 233 young soldiers who died of myocardial infarction.

There is no correlation between obesity and heart disease in countries existing mainly on nonatherogenic diets—mostly carbohydrate and fat derived from vegetables. However, in countries of Western Civilization subsisting on an atherogenic diet high in animal fats, obesity is caused by excess calories derived from fat. Here the correlation between obesity and atherosclerosis is more convincing.

The available evidence strongly suggests that obesity per se, in the absence of hypertension, diabetes, or hypercholesteremia, has no effect on atherosclerosis. That does not mean to imply that obesity correction should not be undertaken in the patient with coronary artery disease or having a high risk of developing it. Such efforts to decrease weight not only reduce the work load of the heart but in the presence of an atherogenic diet contribute to retarding atherogenesis.

PHYSICIAN: It appears that diabetes mellitus even when well controlled accentuates the process of atherosclerosis. Do you have an explanation for this?

DR. KATZ: I am sorry that Dr. Rachmiel Levine is not present today, but I know that Dr. Earl Silber is familiar with his point of view in this regard. Would you undertake to answer this question, Dr. Silber?

DR. EARL SILBER: It is unfortunate that there appear to be few rewards for virtue in the case of diabetes. The incidence of retinopathy, atherosclerosis, and renal glomerulosclerosis are not influenced by the severity of the diabetes, nor by the degree of control. Only neuropathy seems to demonstrate any such gross correlation. The incidence of all but the latter complication appears to be a function of the duration of the diabetic state rather than of the severity or the extent of control. We have frequently observed patients whose diabetes has been rigidly controlled for years, not only as to glycosuria but with respect to the maintenance of normal blood sugars as well, who are blind from retinopathy and have lost limbs from occlusive arterial disease. On the other hand, patients, who are for years vacillating back and forth between insulin shock and diabetic coma, may show virtually no evidence of vascular disease. In one instance a young woman with severe diabetic retinopathy showed, as the only evidence of a disturbed carbohydrate metabolism, a slight delay in return of the blood sugar to normal at the end of 2 hours during the course of a glucose tolerance test. Clinical observations like these of the divergence of the extent of the carbohydrate disturbance and the occurrence of vascular complications have led to the suggestion that in diabetes there are 2 "factors" that may be inherited together, or separately. One the metabolic factor, the other the "vascular factor," if you please. This is largely hypothetical at the present time, but it certainly fits the facts as we encounter them in the clinic.

It is of additional interst, I think, to point out that peripheral vascular disease in the diabetic is arteriolar as well as arterial. In the same way, only in the diabetic does one see atherosclerosis involving the small intramural coronary vessels as well as the major extramural arteries. This, again, is suggestive of a peculiar "vascular factor" in the diabetic.

DR. KATZ: There has been a great deal of interest expressed in our estrogen project in young men following myocardial infarction. Dr. Ben Kaplan has been an important member of this research team since the inception of the program, and I will ask him to summarize the present status of this study.

DR. BENJAMIN KAPLAN: This study, now embracing some 276 patients, primarily men under 50 years after their first myocardial infarction, in a controlled matched study, was begun in 1952. It will take at least another year before sufficient data will be at hand to permit a satisfactory statistical evaluation. Since June 1954 the standard maintenance dosage has been 10 mg. of conjugated equine estrogens (Premarin) daily by mouth. Therapy was begun with 1.25 mg. and gradually built up over 4 months to the full dose. An increase in alpha lipoprotein and phospholipids with a tendency for cholesterol to fall has been consistently

observed. The alpha-lipoprotein level and the presence of gynecomastia are, therefore, employed as reliable indices of patient adherence to the hormone regimen. While the over-all rate of recurrence of myocardial infarction is similar in the 2 groups, the survival rate is higher in the estrogen-treated group. The differences are not yet sufficiently significant statistically. Estrogens have been recently reported as ineffective in the treatment of intermittent claudication and angina pectoris. Favorable results, however, have been reported with prolonged low-dosage estrogen therapy of idiopathic hyperlipemia and hypercholesteremia.

INTERN: I have heard something about a female sex hormone that protects against atherosclerosis but does not produce the feminizing effects. Would you comment on this?

DR. KAPLAN: Efforts are continuing in this direction, but no such compound has as yet been discovered.

PHYSICIAN: Do you have any evidence that adequate treatment of hypertension prevents the progression of or the complications of atherosclerosis?

DR. KATZ: Dr. Schlichter has been interested in the relationship of hypertension to the complications of atherosclerosis for quite some time. I will direct this question to him.

DR. JAKUB G. SCHLICHTER: Animal experiments and clinical studies make it clear that the presence of hypertension accelerates the rate of progression of atherosclerosis. Its reduction, therefore, should retard atherosclerosis. There is at present, however, no clear-cut evidence that the treatment of hypertension with hypotensive drugs significantly alters progression of atherogenesis. On the contrary, it has been pointed out that since antihypertensive drugs are prolonging patients' lives, more and more vascular disease is appearing. This is especially true of disease of the cerebral vessels. This indicates the need for treatment effective for atherosclerosis at the same time as one treats the hypertension. I mean by this that hypotensive drugs should be combined with anti-atherogenic regimens.

DR. KATZ: I would like to direct the participants of this conference to an important subject that has, as yet, not been raised by either the panelists nor the audience, namely anticoagulants.

Blood coagulation bears an important relationship to atherosclerosis. The atheroma itself provides local factors that promote thrombosis. Duguid, from a remarkable series of histologic studies, has suggested that fibrin deposits on the intimal surface of the vessel wall play the central role in the pathogenesis of atherosclerosis. Finally, blood clots serve as the basis for the serious complications of atherosclerosis. Thus, the problems of atherosclerosis, coagulation, and fibrinolysis may all be interrelated. This remains to be established.

Before calling on Dr. Alfred Pick to discuss anticoagulant therapy, I wonder if Dr. Silber would elaborate a bit on the subject of dietary fats and blood coagulation.

DR. SILBER: Since the development of atherosclerosis and coronary heart disease appear to be related to the character of the diet, it is logical to inquire if the diet may not influence thrombosis. Suggestive evidence is to be found in epidemiologic and clinical data as well as from studies of blood coagulation.

The decline in mortality rates from coronary heart disease in many countries during World War II tended to follow reduction in the fat content of the diet. In a number of these countries, the decline in thromboembolic complications after surgery was even more striking than the changes in coronary heart disease. Moreover, it has been recognized for a number of years that posttraumatic thrombosis and embolism, as well as coronary heart disease, are uncommon in populations habitually subsisting on low-fat diets.

From a clinical point of view it has long been known that thrombosis is common in certain clinical disorders in which lipemia is a conspicuous finding. The occurrence of coronary thrombosis after the ingestion of a heavy meal has been familiar to clinicians for years, but only recently has it been suggested that this may be due to hypercoagulability of the blood induced by alimentary lipemia.

The addition of small amounts of food fats

to blood in vitro greatly accelerates coagulation, but there is much controversy about the coagulation of blood drawn during the lipemic phase after a fatty meal. Despite the unsatisfactory state of present methods for the quantitative study of blood coagulation, the consensus of published data indicates that when blood is drawn after a fatty meal: (1) the clotting time in plain glass is not consistently changed; (2) the silicone clotting time is frequently shortened; (3) the Stypven time is markedly shortened; clearly, postprandial hypercoagulability can be demonstrated in vitro by some tests, but there is, as yet, no evidence that these observations are relevant to the initiation of coronary thrombosis. On the contrary, in vitro coagulation tests failed to demonstrate any important difference between patients and control subjects.

Many believe that intravascular coagulation is a dynamic process with small fibrin strands being continually deposited on vascular endothelium and the natural process of fibrinolysis removing these deposits. Obviously, from such a point of view, inhibition of lysis could produce the same result in blood vessels as would the development of hypercoagulability. The finding, therefore, that normal fibrinolytic activity is inhibited by a fatty meal assumes great importance.

In summary, a variety of evidence points toward an unfavorable effect of high-fat diets and postprandial hyperlipemia on susceptibility to thrombosis. Any conclusions, however, must await the results of more research with improved methods.

DR. KATZ: Thank you, Dr. Silber. Dr. Alfred Pick has been concerned in a major way with the studies in our department relating to myocardial infarction. We are all aware that the cooperative study of the Committee on Anticoagulant Therapy of the American Heart Association showed that the immediate mortality from acute coronary occlusion was roughly halved by anticoagulant therapy. Michael Reese, I might add, was one of the original cooperating institutions in that study and contributed one eighth of the patients. I think it is fair to say that the validity of their conclusions has not been seriously challenged by comparable data from subsequent investigators. Dr. Pick, will you conclude the discussion on coagulation and atherosclerosis by defining the place of the long-term use of anticoagulants in the treatment of these diseases? If your comments stir up a hornet's nest of controversy, I promise to come to your rescue.

DR. ALFRED PICK: This is an important problem because the practicing physician wants to know if the extra effort involved for the patient and doctor is merited. I should add, not only extra effort, but added risk and expense as well. It is not easy from our experience, and from the many reports that have originated elsewhere, to evaluate completely the effectiveness of such treatment. The difficulty arises from the fact that the effects have been assessed by comparing mortality rates in treated versus untreated patients. Such a method demands large series of patients, matched control groups, and long periods of observation. On one or more of these scores, no study of this problem has completely escaped criticism.

The results have been sufficiently uniform in their encouraging results to stimulate better designed studies here and abroad. It is a fair summary of previous work to say that the mortality rate in the patients so treated was one third to one fourth that of control patients. That is certainly more impressive than the results to which Dr. Katz alluded with respect to the short-term treatment of recent myocardial infarction.

The Medical Research Council of Great Britain has very recently reported on a carefully controlled 3-year clinical study of long-term anticoagulant therapy following myocardial infarction. The indices of the effectiveness of the treatment were 3-fold: namely death from all causes attributable to cardiovascular disease and from recurrent myocardial infarction in particular; frequency of recurrent myocardial infarction; and, lastly, data relating to the ability of the patient to return to work, and the presence or absence of angina or dyspnea at the time of the last examination.

The difference in the gross mortality during the follow-up period was not statistically significant in the treated and untreated groups. However, when infarcts serious enough to cause permanent withdrawal from the study were added to deaths as a combined index of therapeutic success or failure, there was a significant reduction in their frequency in these men. Under 55 years of age, treated men experienced recurrent infarction at 20 per cent of the rate of the controls; over that age the rate was halved in the treated group. The difference in the death rate of the 2 groups was most evident in the first 6 months of the follow-up period, but the disparity in the reinfarction rate was maintained for at least 2 years.

Admittedly, I am in a dilemma when I am asked about the experience of this hospital. As an electrocardiographer I am impressed by the fact that in recent years, roughly coincident with the introduction of anticoagulants as a routine procedure in acute myocardial infarction, the typical textbook evolution of the electrocardiogram has become rarer, and a protracted course, with long persistence and recurrence of injury effects has become quite common. I am also impressed by the failure of anticoagulants in many cases to prevent the progression of localized ischemic T inversions to signs of extensive transmural infarction. The pathologic substrate of these electrocardiographic phenomena is unknown. This problem surely deserves serious study. On the other hand, as a clinician, I cannot overlook the favorable mortality statistics and I wonder seriously whether long-term anticoagulant therapy should become as much, or more, a part of the management of the coronary patient as dietary or hormonal treatment. Is this heresay or confusion?

There can, however, be no doubt that ambulant anticoagulant therapy can, if improperly carried out, be an agent of more harm than good. The first prerequisite is a competent laboratory to carry out accurate prothrombin time tests. Second, one needs an intelligent, cooperative patient; the final ingredient is an alert, informed physician who is prepared to give the extra effort required to keep these patients out of trouble. If any of the 3 is lacking, it is foolhardy to undertake such treatment.

DR. KATZ: Thank you Dr. Pick for your usual forthright approach. Judging from the audience reaction you seem to have squelched heated debate. I think you have made a sale.

PHYSICIAN: Dr. Pick, which is better anticoagulant therapy: heparin or the coumarin drugs?

DR. ALFRED PICK: I was afraid this question would be raised—afraid because I am an electrocardiographer and a cardiologist, not a hematologist. The answer to your question is enormously complicated and, certainly speculative, at present. At the risk of getting in over my head, let me just point out one aspect of the problem you have raised. Dicumarol inhibits factor VII in the clotting scheme. That is, it is largely antithromboplastic. It appears that heparin exerts its effect primarily by inhibiting Christmas factor. The latter appears to play a role in imparting "stickiness" to platelets. It would, therefore, seem to be potentially involved in any considerations of a "hypercoagulable" state of the blood which is coming to the fore in the area of atherosclerosis and thrombogenesis. The differences in action between heparin and the coumarins may prove to be of major significance as more information becomes available from the hematologist's laboratory. Luckily, the problem is readily resolved now because heparin cannot be given orally. I have no comment to make on sublingual heparin.

DR. KATZ: Dr. Silber do you want to reenter this discussion?

DR. SILBER: No, sir, I will heed Dr. Pick's warning about getting in over one's head.

DR. KATZ: Time is growing short, and I would like to direct the attention of the panelists to the problem of smoking and its effect on the cardiovascular system. Advertizers for the multimillion dollar cigarette industry exploit every medium for reaching the public to extoll the joys and glory of tobacco. Snob appeal for the feminine fancy and insinuated virility for the masculine mind are

but 2 of the psychologic approaches used to "push the product." On the other hand, with reports of increased mortality from lung cancer and heart disease associated with cigarette smoking, it behooves the physician to reexamine critically the controversial facts. It is to be expected that the public will look to the physician for a rational attitude in this matter. I trust the audience will appreciate that I find it irresistible to ask Dr. Mack to "filter" the facts for us and dispel the haze of smoke that surrounds the subject. Specifically, Dr. Mack, is there evidence that cigarette smoking causes atherosclerosis or influences the course of coronary heart disease?

DR. IRVING MACK: The epidemiologic studies answer in the affirmative and there is a considerable body of physiologic data to support this impression. The former approach, despite the many difficulties inherent in such studies, indicates a strong difference between cigarette smokers and nonsmokers on coronary heart disease mortality. An excess number of deaths from coronary heart disease of from 1 to 7 persons per 1,000 men per year is found in heavy cigarette smokers as compared to nonsmokers. Moreover, coronary artery disease seems to occur more frequently and at an earlier age in the person who smokes heavily than in the nonsmokers. Likewise, the mortality rate is higher among younger persons with coronary disease who are smokers than among nonsmokers. While the facts are beyond dispute, their meaning is not clear. They may represent the disclosure of a particular personality type which needs to smoke excessively and at the same time has more coronary disease. Or they may represent cause and effect. Nevertheless, heavy cigarette smoking should be discouraged.

From a physiologic point of view smoking has definite measurable effects on the peripheral circulation and the heart itself. Smoking causes constriction of the peripheral blood vessels in the normal subject. The effect is exaggerated in those with peripheral vascular disease. A modest elevation in blood pressure occurs. Complete tolerance does not develop to these vascular effects, nor are they abolished by alcohol. It is no longer controversial, but an established fact that smoking leads to progression of some peripheral vascular disease, and abstinence from tobacco is beneficial and is a primary principle in the treatment of such cases.

The acute effects of tobacco on the heart are an appreciable increase of the pulse rate; an increase in the work of the heart; and flattening of the T waves of the electrocardiogram. The latter changes probably originate from increase in heart rate secondary to increased sympathetic tone. Increased adrenal secretion may be a factor when these electrocardiographic changes occur without a change in rate.

One of the most interesting phenomena is the deterioration of the ballistocardiogram seen in patients with coronary disease after smoking. It is thought that these changes are the result of occult or overt inadequacies in myocardial function elicited by peripheral vasoconstriction. While the ballistocardiograph cannot be considered ready for use in clinical diagnosis, it has provided an interesting research method. Its further refinement may some day establish it as a practical tool of limited extent.

From studies of the electrocardiograms and ballistocardiograms of normal subjects after smoking it has been suggested that tobacco heart or "tobacco angina" may not be due to underlying heart disease, but may be a definite clinical entity resulting from functional derangement of this organ due to nicotine.

MEDICAL RESIDENT: Is any different effect observed after smoking king-sized or filter cigarettes as compared to "regulars?"

DR. MACK: None that I know of.

DR. KATZ: There are a number of interesting facets to the problem of atherosclerosis that lack of time denies discussion, such as the influence of physical activity and emotional stresses on atherosclerosis, or of such therapeutic measures as I^{131} and revascularization surgery. The hour is almost at an end, and, if I may be permitted, I will summarize for my colleagues and myself.

The thesis today has not been that diet is

the only factor in the development and persistence of atherosclerosis but that it influences both atherogenesis and thrombogenesis. Moreover, it is an important part of the reason for the differences in frequency of coronary heart disease between populations. Those who deny this must admit that no such similar consistency to explain these differences can be found in terms of race, climate, use of tobacco, emotions, habitual physical activity, urbanization, and so on. Hypertension, hypercholesteremia, and obesity are factors to be reckoned with in the development of atherosclerosis.

In our present state of knowledge, a low-fat diet of sensible degree, with an increase in the ratio of unsaturated to saturated fat is a key step in the prophylaxis and treatment of the basic process of atherosclerosis and its sequelae. Unsaturated fats should be substituted in the diet not supplemented to it. The beneficial effects of all hypocholesteremic agents in atherosclerosis is still unsettled, although sitosterols appear to be the most appropriate adjuvant for clinical use with the appropriate diet.

Long-term anticoagulant therapy is beginning to emerge as an important therapeutic advance in the treatment of cerebral as well as coronary atherosclerosis. A better understanding of blood coagulation looms as an important step forward in controlling the complications of atherosclerosis. Indifference to smoking is no longer warranted by the patient or physician.

The physician must begin to classify patients into low- and high-risk groups as far as the appearance of clinical manifestations of atherosclerosis is concerned. He can no longer stand by when he is dealing with a high-risk patient. Risk is increased by obesity, hypertension, hypercholesteremia, diabetes, renal disease, and by a "bad" genetic background.

Many of the questions raised here are still far from settled, but the problem of atherosclerosis is one that holds promise of giving ground before the combined efforts of the investigator and the clinician.

Finally, may I thank all of you for being so rapt an audience.

Summario in Interlingua

Iste documento es un processo verbal de un conferentia de multiple participantes discutente varie aspectos del problema de atherosclerosis ab le puncto de vista de su gerentia clinic. Le objectivos del conferentia esseva formulate sequentemente per su preside: (1) Presentar al clinico practic un summario de factos relative al pathogenese de atherosclerosis le quales es ben establite e le quales es significative in consequentia de lor applicabilitate al caso individual. (2) Proponer un programma prophylactic specific super le base de tal ben-establite factos. (3) Delinear un programma therapeutic pro le patiente con evidentia clinic de atherosclerosis o su sequellas. Le sphera thematic del conferentia non includeva infarcimento myocardial e angina de pectore.

Symposium On Coronary Heart Disease
To Begin in August 1960 Issue

ABSTRACTS

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PULMONARY DISEASES

Gray, F. D., Jr., and Field, A. S.: The Use of Mechanical Assistance in Treating Cardiopulmonary Disease. Am. J.M. Sc. **238**: 146 (Aug.), 1959.

Two machines useful as mechanical aids to ventilation are described. The first is a rhythmically inflated abdominal belt functioning alternately with mouth inspiratory positive pressure. This apparatus provides a forced expiration in contrast to the passive expiration of inspiratory positive pressure breathing therapy alone. This mechanism increases alveolar ventilation and is useful in patients with severe pulmonary emphysema. It maintained the blood pressure in 1 patient with vasomotor instability. The second apparatus provides alternate and rhythmic electrical neuromuscular stimulation of the diaphragm and lower abdominal muscles. This is a more difficult machine to use. It also provides adequate ventilation in emphysematous patients. It shows promise as an instrument useful in initiaiting diaphragmatic breathing exercises in those patients whose disease has impaired diaphragmatic motion.

SHEPS

Hurlimann, J., Raymond, A., Desbaillets, P., and Rivier, J. L.: So-Called Essential Pulmonary Hypertension. Cardiologia **34**: 327, 1959.

A case is reported of a 28-year-old woman afflicted with pulmonary hypertension who had gone through 1 pregnancy and 1 miscarriage. Histologic studies of the pulmonary arterioles with graphic reconstruction of series of the sections revealed polypoid fibrous vascular obstructions resembling small emboli. The authors suggest that postpartum pulmonary hypertension, which has been presumed to be primary, may in fact be secondary to small pulmonary mieroemboli.

KARPMAN

Semisch, R.: New Points of View concerning the Hemodynamics of Pulmonary Circulation on the Basis of Pulmonary Angiographic Findings. Ztschr. Kreislaufforsch. **48**: 437 (May), 1959.

Injection of 5 to 6 ml. of 76 per cent Urografin into a pulmonary arterial catheter in the wedge position enabled visualization of the terminal subsegmental arteriolar, capillary, and venous systems 1.5 to 2.5 seconds after injection. After 1 or 2 minutes the dye in the venous system became diluted, but the arterial and capillary systems remained filled as a "stationary angiogram" if the position and pressure of the catheter were not changed. Withdrawal of the catheter caused all dye to disappear. The observation that the stationary angiogram showed a smaller diameter of the arterioles than the immediate angiogram was interpreted as signifying that the increased oxygen saturation of the stationary venous and capillary blood caused a reflex arteriolar constriction. The purpose of this constriction could be to prevent a higher pulmonary flow than is necessary for complete saturation of capillary blood, and pulmonary arteriovenous anastomoses are considered as safety valves preventing excessive pulmonary hypertension. These anastomoses could be seen in terminal angiograms, especially in pulmonary emphysema, where capillary flow is diminished. The reduction in angiographic capillary filling can be used to assess the severity of pulmonary emphysema.

LEPESCHKIN

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Cicero, R., Mendez, C., Aceves, J., and Mendez, R.: Recovery of the Heart after Arrest with Potassium Citrate. Arch. Inst. cardiol. México **29**: 421 (July-Aug.), 1959.

The recovery of the physiologic properties of the heart was studied after the production of cardiac arrest by potassium citrate in isolated dog hearts perfused by a donor dog. During cardiac standstill the heart showed no mechanical or electrical activity. When the excess of potassium was washed out from the heart and perfusion with the donor dog reestablished, the physiologic properties of cardiac tissues recovered generally during the first 15 minutes. The return to control values occurred in the following order: ventricular and atrial conduction velocity; ventricular and atrial excitability, and conduction velocity of the atrioventricular system and refractory periods of the atrium, ventricle, and atrioventricular system. Cardiac contractility usually recovered in 2 stages, an initial rapid one, followed by a period of slower recovery. In some cases, once the perfusion was reestablished, the heart fibrillated or showed relative failure. This was much more evident when excessive doses of potasium citrate were used to induce cardiac arrest. When the heart showed poor contractility after an excessive dose of potassium citrate, its properties recovered with more difficulty. In such cases the use of drugs such as norepinephrine and calcium chloride had a temporary effect on heart rate and contractility; strophanthidin had a more lasting effect upon contractility, and barium chloride had a considerable effect on the automatic properties of the heart. This last drug initiated automatism in some cases in which automatic activity did not recover after coronary perfusion; contractility was increased in a more evident and lasting fashion.

BRACHFELD

Holland, W. C., and Briggs, A. H.: Fibrillation and Potassium Influx. Science **129**: 212 (Jan. 23), 1959.

Fibrillation was induced by electric stimulation of isolated rabbit atria suspended in low-potassium media in the presence of acetycholine. The influx and efflux of K^{42} was measured in various experimental situations. Acetycholine increased both influx and efflux of potassium, whereas during fibrillation only an increase in efflux was obtained and influx remained essentially unchanged. Thus the authors propose that the changes induced by acetylcholine result from an increase in membrane permeability to potassium that apparently does not occur during fibrillation. They conclude that an inhibition of active potassium uptake is not involved in the initiation of fibrillation and that the process results from a marked increase in sodium permeability.

KARPMAN

Milton, A. S.: The Relation between Temperature and Changes in Ion Concentration on Ventricular Fibrillation Induced Electrically. Brit. J. Pharmacol. **14**: 183 (June), 1959.

Electrically induced ventricular fibrillation was studied in the isolated rabbit heart during coronary perfusion with various solutions and at various temperatures. Fibrillation was promoted by lowering the sodium or potassium concentration of the perfusate, by raising the calcium concentration, and by maintaining higher temperatures up to 37 C. These conditions were also associated with an increase in amplitude of the nonfibrillating heart beat. Therefore, it seemed likely that an increased oxygen requirement contributed to effecting spontaneous fibrillation. It was suggested that experiments involving perfusion of the whole heart be done at temperatures of 32 C. or lower.

ROGERS

Strauss, M. B., and Papper, S.: Sodium and Water Retention in Chronic Congestive Heart Failure. J. Chron. Dis. **9**: 536 (May), 1959.

Sodium retention in congestive failure appears to be more dependent on the extent of tubular sodium reabsorption than on a reduction in glomerular filtration rate. Knowledge is lacking of many of the mechanisms by which body sodium content is altered in various states of health and disease, but certain concomitants of congestive heart failure, such as malnutrition, hypoxia, and distortions of the intrarenal circulation, may play a significant part. Over-all volume of body fluids is not the sole factor in sodium retention, since a change of body position can affect sodium excretion. Tubular sodium reabsorption is increased by standing or wearing cuffs about the thighs to pool blood and extracellular fluid volume in the legs. Lying down has the opposite effect, as does the closing of an arteriovenous fistula. Water retention, or hyponatremic edema, in the patient with congestive heart failure, is probably caused by an altered "set" of the mechanisms that control antidiuretic hormone release and the sense of thirst. Treatment with strong salt solution or water restriction or both may be helpful. As a rule, however, greater benefits follow an improvement of myocardial function by giving a little more, or perhaps a little less, digitalis, control of infection or thyrotoxicosis, or greater limitation of the patient's activity.

MAXWELL

Vaughan Williams, E. M.: The Effect of Changes in Extracellular Potassium Concentration on the Intracellular Potentials of Isolated Rabbit Atria. J. Physiol. **146**: 411 (June 11), 1959.

The author studied the effect of changes in the external potassium concentration on the resting potential and on the rate of repolarization of the action potential in isolated rabbit atria. In potassium concentrations between 4 and 11 mM, the calculated regression relating resting potential to potassium concentration had a slope of 56.03± 1.77 mV per 10-fold change in potassium. Repolarization was faster in solutions where the potassium concentrations were either low (1.0 to 3.5 mM) or high (10 to 11 mM) as compared to solutions where the concentrations were 5 to 6 mM. The resting potentials remained stable at each potasium concentration for as long as 3 hours, and there was no tendency to revert towards "normal" if the external potassium were changed.

KARPMAN

REVIEWS IN CARDIOVASCULAR DISEASE

Dustan, H. P., Page, I. H., and Poutasse, E. F.: Renal Hypertension. New England J. Med. **261**: 647 (Sept. 24), 1959.

Goetz, R. H.: Clinical Aspects of Vascular Reactivity. Surg., Gynec. & Obst. **109**: 209 (Sept.), 1959.

Heyman, F.: Transmission of Atrial Waves to Peripheral Arteries in Complete Heart Block and Atrial Flutter in Man. Acta med. scandinav., Suppl., **164**: 344, 1959.

Shearn, M. A.: The Heart in Systemic Lupus Erythematosus. Am. Heart J. **58**: 452 (Sept.) 1959.

Wagener, H. P.: Measurement of Retinal Arterial Pressure. Am. J. M. Sc. **238**: 211 (Aug), 1959.

Zeh, V. E.: Die Diagnose der Trikuspidalinsuffizienz. Arch. Kreislaufforsch. **30**: 129 (July), 1959.

RHEUMATIC FEVER

Brest, A. N., Uricchio, J., and Likoff, W.: Valvular Surgery in the Young Patient with Rheumatic Heart Disease. J. A. M. A. **171**: 249 (Sept. 19), 1959.

An appraisal has been made of the results of valvular surgery in 37 rheumatic patients under 20 years of age. In the past it has been assumed that surgery for rheumatic heart disease should be limited to older patients because of the supposed risk of reactivating the rheumatic infection. No reactivation occurred in any patient reported here and thus it would appear that indications for cardiac surgery in the younger patients are essentially the same as those applied to older persons and should not be influenced by the factor of age with the fear of recurrence of rheumatic activity.

KITCHELL

Elster, S. K., and Pader, E.: Studies on Acute Rheumatic Fever in the Adult. II. The Rebound Phenomenon. Ann. Int. Med. **51**: 339 (Aug.), 1959.

In a group of 43 adult patients treated for acute rheumatic fever clinical or laboratory evidence of "the rebound phenomenon" appeared in 22 patients. The rebound phenomenon was defind as the occurrence of any 1 of the following manifestations upon reduction or discontinuation of suppressive drug therapy: fever, elevation of the erythrocyte sedimentation rate, reappearance of C-reactive protein in the blood, arthralgia, arthritis, chest pain, electrocardiographic abnormalities, pericarditis, or congestive heart failure. Of the 22 patients, 14 had 1 rebound, 7 had 2 rebounds, and 1 had 4 rebounds. Fever, arthralgia, and tachycardia were the most common clinical manifestations, with arthritis and pericarditis occurring less frequently. Elevation of the erythrocyte sedimentation rate, reappearance of C-reactive protein were the most frequent laboratory findings. No obvious correlation was found between the rebound phenomenon and the dose or type of drug used for treatment. Salicylates, adrenocortical hormones and a combination of salicylates and hormones were used as treatment. The duration of illness prior to therapy, the duration of therapy, and the mode of withdrawal of the drug did not appear to influence the incidence of the rebound phenomenon. In all patients, reinstitution of therapy was effective in controlling the manifestations. The authors believe that the rebound phenomenon is an indication of persistent rheumatic activity and requires prompt therapy.

KAYDEN

Lannigan, R.: The Rheumatic Process in the Left Auricular Appendage. J. Path. & Bact. **77**: 49 (Jan.), 1959.

A series of 175 biopsy specimens of left atrial appendages removed at mitral valvulotomy revealed all stages in the development and retrogression of rheumatic lesions. Collections of mucopolysaccharides in the tissue spaces were apparently the earliest lesions. Aschoff nodules were found in the later stages of the rheumatic process and were usually associated with less mucopolysaccharide deposition than was present in the early lesions. Active lesions were found in 64 per cent of the 175 biopsies, whereas the early nonspecific changes occurred in only 9 biopsies. The author concluded that since 47 per cent of

the patients in the series had no history of acute rheumatic fever and all of them had been investigated prior to operation to exclude clinically active disease, it would appear that acute rheumatic fever is only an episode or a series of episodes in a long-continued subclinical disease.

KARPMAN

Lendrum, B. L., Simon, A. J., and Mack, I.: Relation of Duration of Bed Rest in Acute Rheumatic Fever to Heart Disease Present 2 to 14 Years Later. Pediatrics **24**: 389 (Sept.), 1959.

Three-hundred and sixty children from the Herrick House in Bartlett, Illinois, were followed from 2 to 14 years after an episode of rheumatic fever. Increasing activity was allowed these children immediately after certain physical findings and laboratory studies (especially temperature, sleeping, pulse rate, leukocyte count, erythrocyte sedimentation rate) approached normal limits. Most of the children were advanced to unlimited physical activity within 2 to 5 months. The authors conclude after thoroughly examining these patients 2 to 14 years after the initial episode of rheumatic fever that prolonged bed rest and restriction of activity after an acute attack of rheumatic fever were not necessary for optimal healing of the injured heart; in fact, the results suggested that the effect of early activity may have been beneficial rather than deleterious.

KARPMAN

Stahlman, M. T., and Denny, F. W., Jr.: The Prophylaxis of Streptococcal Infections in Patients with Rheumatic Fever. J. Dis. Child. **98**: 66 (July), 1959.

Fifty children with acute rheumatic fever were randomly divided into 2 groups; 1 group was placed on sulfadiazine (0.5 Gm. twice daily) and the other group was placed on erythromycin (100 mg. twice daily). These patients were followed for an average of 19½ months, and it was observed that 7 patients in the sulfadiazine group had positive cultures for group A streptococci whereas there was only 1 such patient in the erythromycin group; 1 patient in the sulfadiazine group developed a recurrence of rheumatic fever. The authors concluded that erythromycin appeared to be superior to sulfadiazine in their study and that it more nearly satisfied the criteria for an ideal long-term prophylactic agent against group A streptococcal infections in patients who have had rheumatic fever.

KARPMAN

ROENTGENOLOGY

Amplatz, K., Ernst, R., Lester, R. G., Lillehei, C. W., and Lillie, A.: Retrograde Left Cardioangiography as a Test of Valvular Competency. Radiology **72**: 268 (Feb.), 1959.

To the present time there has been no simple or reliable method for differentiating mitral stenosis from mitral insufficiency. In the presence of mitral insufficiency curves made at left heart catheterization, with pressure and flow measurements, have been difficult to interpret. The authors used a special catheter, which was introduced by way of the femoral artery, passed into the left ventricle, and placed in the apex. The opaque medium was slowly injected during a period of at least 4 consecutive systoles. In pure mitral stenosis there was no opacification of the left atrium. With mitral insufficiency the opaque medium accumulated in the left atrium and stained it more densely than the left ventricle and the aorta. It was thought that the degree of opacification correlated directly with the degree of mitral insufficiency.

KITCHELL

Astley, R., Parsons, C. G., and D'Abreu, A. L.: Cineangiocardiography. Proc. Royal Soc. Med. **52**: 457 (June), 1959.

The indications for and the technics used in cineangiocardiography are described and 109 cineangiocardiograms, which included 14 different conditions, are analyzed. The method was particularly useful in diagnosing patent ductus arteriosus in infancy before serious symptoms develop and is urged for every baby with symptoms of a left-to-right shunt. In this series 14 infants had this condition. The intermittent contrast filling and emptying of the pulmonary artery (left oblique position) was characteristic. In infancy, the method's greatest value lies in differentiating septal defects from a patent ductus arteriosus. Following a venous injection in the left oblique position, a dilution defect is seen in the contrast medium in the right atrium or ventricle, indicating the shunt in a simple septal defect. After infancy, cineangiocardiography employed with cardiac catheterization and selective injections will show the location and often the size of septal defects. The right oblique position was preferred for demonstrating valvular, infundibular, or combined stenosis, by a venous or selective injection. An electrocardiographic tracing, combined with cineangiocardiography, makes possible the identification of as many as 10 shunts within 3 seconds, as illustrated in the article. The method was found to be safe and accurate.

MAXWELL

Blankenhorn, D. H., and Stern, D.: Calcification of the Coronary Arteries. Am. J. Roentgenol. **81**: 772 (May), 1959.

It has been possible to estimate the luminal diameter of the coronary arteries in living man by arteriography, but the technic is not well suited

to routine use and its application is limited because of the hazards involved. In a search for a simpler method, the authors studied 76 hearts post mortem by making roentgenograms of the heart placed directly on an x-ray film. Sixty-one, 80 per cent, showed calcific deposits in the coronary arteries. Coronary calcifications were the most frequent encountered intracardiac radiopaque lesions and were more commonly present than absent in patients over 40 years of age. The most common calcific coronary lesions were 1, 2, and 3 mm. punctate densities, which occurred in groups of 2 to 4 in the proximal portions of the artery. Since coronary calcification has been shown to appear in patients 40 to 60 years of age, there is hope that a roentgenographic method, if discovered, might be useful at a time of life before atherosclerosis has led to ischemic heart disease.

KITCHELL

Boblitt, D. E., Figley, M. M., and Wolfman, E. F., Jr.: Roentgen Signs of Contrast Material Dissection of Aortic Wall in Direct Aortography. Am. J. Roentgenol. **881**: 826 (May), 1959.

Translumbar aortography, although widely employed and of great value in clinical appraisal of vascular diseases, is not a simple diagnostic procedure. One complication of this method is the inadvertent injection of contrast material into the wall of the aorta rather than into the lumen of the vessel itself. The roentgen signs of this intramural injection of contrast material are described and the importance of their recognition by everyone performing direct aortography is stressed. In 425 translumbar aortographies intramural injection of some degree occurred in 42 patients. In 3 of these, death resulted either directly or indirectly from the intramural injection, 2 of the patients dying with proved dissecting aneurysms. The other 39 patients of this group had no significant complications. When direct aortography is complicated by an intramural injection the procedure should be discontinued and not attempted for at least 24 hours.

KITCHELL

Campeti, F. L.: Cinecardiometry and Cine-Electrokymography: New Angiographic Techniques for the Analysis of Cardiac Mechanics. Am. J. Roentgenol. **81**: 778 (May), 1959.

Cardiac mechanics and hemodynamics can be analyzed directly from high-speed cineangiocardiographic records. Cinecardiometry represents graphically the motion of the cardiovascular anatomic structures opacified by contrast medium. The silhouettes of heart chambers and great vessels are precisely drawn directly from the projected images of each frame of the cineangiocardiogram. Diameters and areas are measured chronologically, and volumes of the cardiac cavities are calculated. Densitometry is a photometric method for recording the angiographic density of the cardiovascular structures from each consecutive frame of the cineangiocardiogram. Thus the progression and distribution of the contrast medium peripherally injected into the great vessels and cardiac cavities can be measured. Cineelectrokymography and cinedensitometry are electrokymographic technics for recording the border motion and the density changes of the cardiovascular structures whether opacified or not by contrast medium. Correlation of tracings recorded with these methods and electrocardiograms, pressures, pneumograms, and so forth, recorded synchronously can represent the cardiac performance in each phase of the cycle. The applications of these methods to cardiovascular investigation and diagnosis are considered.

KITCHELL

Castelanos, A., Garcia, O., Gonzales, E., and Pereiras, R.: Thoracic Aortography versus Levoangiocardiography. Am. J. Roentgenol. **82**: 403 (Sept.), 1959.

Levo-angiocardiography obtained by the intravenous injection of contrast medium was compared with thoracic aortography. To obtain a satisfactory levo-angiocardiogram the bolus of contrast medium must be injected within 1 second in high concentration and in an adequate amount. If a left-to-right shunt exists the visualization of the thoracic aorta with a contrast medium was often diminished or unsatisfactory with the levo-angiocardiography technic. When visualization of the left heart, the aorta, and demonstration of abnormal communications between the left heart and aorta were desired, in most instances thoracic aortography gave more and better information than the levo-angiogram. The former technic in experienced hands was not associated with greater mortality of morbidity than the latter.

KRAUSE

Davis, J. G., and Winsor, P.: Roentgen Findings in Aneurysm of the Descending Thoracic Aorta. Am. J. Roentgenol. **81**: 819 (May) 1959.

Seven cases of aneurysm of the descending thoracic aorta are reported. Three of these were syphilitic and 4 arteriosclerotic. Four cases were subjected to thoracotomy, 2 having been correctly diagnosed by roentgen findings. The remaining 2 cases were incorrectly diagnosed as bronchogenic cyst and bronchogenic carcinoma respectively prior to surgery. In the remaining 3 cases correct diagnosis was made on routine roentgenographic

examinations. The authors point out that with advances in vascular and thoracic surgery the differentiation of aneurysms from other intrathoracic lesions takes on added significance. Roentgen studies including retrograde aortography, angiocardiography, and laminography will in most instances establish the diagnosis of aneurysm of the descending thoracic aorta.

KITCHELL

Fabrikant, J. I., Anlyan, W. G., Baylin, G. J., and Trumbo, R. B.: A Comparison of Techniques for Visualization of the Coronary Arteries. Am. J. Roentgenol. **81**: 764 (May), 1959.

Various technics of coronary arteriography were compared in a colony of 46 mongrel dogs. Injections of Hypaque with an automatic injector through an intraarterial catheter with the tip located at the junction of the brachiocephalic artery and the ascending aorta consistently produced adequate visualization. The technic was improved by the use of temporary acetylcholine cardiac arrest. Electrocardiographic monitoring, serum transaminase determinations, and histologic examinations showed no significant alterations following these procedures and no added hazard with the use of acetylcholine arrest.

KITCHELL

Gribbe, P., Hirvonen, L., Lind, J., and Wegelius, C.: Cineangiocardiographic Recordings of the Cyclic Changes in Volume of the Left Ventricle. Cardiologia **34**: 348, 1959.

The volume of the left ventricle both at the period of isometric contraction and at the end of the ejection phase was calculated from 31 angiograms performed on 25 dogs. At the termination of the ejection phase, the residual blood volume was estimated and the stroke volume was calculated by taking the difference between the minimal and maximal volumes of the left ventricle. The mean value for the stroke volume was found to be 60.4± 3.4 per cent (with a range of 55-66 per cent) of the end diastolic volume of the left ventricle.

KARPMAN

Guzman, S. V., and West, J. W.: Cardiac Effects of Intracoronary Arterial Injections of Various Roentgenographic Contrast Media. Am. Heart J. **58**: 597 (Oct.), 1959.

The cardiac effects of various radiopaque dyes were studied in dogs following intracoronary arterial injection Urokon, Hypaque, Cardiografin Renografin, and Diodrast (in the descending order of effectiveness) were found to induce cardiac arrhythmias, to produce ST-T wave changes in the electrocardiograms, to depress the contractile force of the heart, to cause a drop in blood pressure, and to increase the coronary blood flow.

SAGALL

Hoeffken, W.: Angiocardiography with Carbon Dioxide. Fortschr. Röntgenstr. **91**: 151 (July), 1959.

Experiments in dogs showed that rapid injection of 50 ml. of CO_2 (2.5 per cent of cardiac minute volume) for the purpose of visualization of cardiac cavities caused only insignificant side effects, while injection of 200 ml. was lethal. In man, injection of 100 ml. (2.5 per cent of minute volume) through the cubital vein was sufficient for diagnostic purposes but led to no unpleasant side effects; a machinery murmur was heard over the heart for about 20 seconds and the first inspiration after the injection was especially deep. The electrocardiogram showed no change. The injection should not be repeated until roentgen examination shows that any residual bubbles have been absorbed. Possible complications can be minimized by left lateral position of the patient. The method allows detailed visualization of the walls of the vena cava (recognition of infiltration, compression, or thrombosis), and of the right atrium and ventricle (recognition of hypertrophy and dilatation, pericardial fibrosis, aneurysms, tumors, or thrombosis as well as changes in the configuration of tricuspid and pulmonary valves). It should not be used when there is possibility of right-to-left shunt or coronary disease, and should be used with great caution in overload of the right heart.

LEPESCHKIN

Keats, T. E., and Martt, J. M.: Acyanotic Tetralogy of Fallot. Am. J. Roentgenol. **82**: 417 (Sept.), 1959.

Four patients, aged 4, 7, 37, and 52 with acyanotic tetralogy of Fallot are described. The over-all incidence of the acyanotic form of the disease is reported as 10 per cent. Such patients may have a mild or moderate pulmonary stenosis with a small or moderate ventricular septal defect. This results in a balanced hemodynamic effect. Others may have dominant ventricular septal defect with a mild infundibular stenosis. This will cause a large left-to-right shunt with an increased pulmonary blood flow. Finally, some may have a dominant pulmonary stenosis. This is usually associated with a small ventricular septal defect and results in a right-to-left shunt. In the classic form the roentgen appearance of the heart reveals a blunted, uptilted apex, concavity of the pulmonary segment, and hypovascu-

lar lung fields. However, cardiac catheterization data and roentgenograms are presented to confirm the variability of the tetralogy depending upon which lesion is dominant, the pulmonary stenosis or the ventricular septal defect, or whether these lesions "balance" each other.

KRAUSE

Lehman, J. S., Boyer, E. A., and Winter, E. S.: Coronary Arteriography. Am. J. Roentgenol. **81**: 749 (May) 1959.

With presently developing attempts at direct surgical attacks on lesions of the coronary arteries, effective roentgen methods for visualization of the coronary artery system have become increasingly important. In some patients excellent results have been obtained by the use of catheter thoracic aortography. The coronary arteries have also been opacified by transthoracic needle puncture of the left or right ventricle. More recently a procedure termed suprasternal thoracic aortography has been employed. With this method the ascending aorta is punctured via a suprasternal insertion, the needle tip is advanced to a position slightly above the aortic sinuses, and radiopaque medium is inserted rapidly. In some studies cardiac arrest has been induced pharmacologically by acetyl choline in conjunction with catheter or with suprasternal thoracic aortography. It has become apparent that roentgenologic demonstration of coronary arteries can be accomplished by several methods although none currently available are entirely satisfactory. In experimental animals good results have occasionally been obtained with the use of simultaneous catheter balloon occlusion of the ascending aorta and cardiac arrest. Simultaneous biplane rapid-serial filming during such arteriography is to be preferred to single plane-film study, and cinefluorography would appear to offer an added advantage. There are many technical difficulties in such studies but there is a genuine need for a technic that is efficient, reliable, and without appreciable hazards.

KITCHELL

Lyons, H. A., Strober, M., McFetridge, J. S., and Caro, C. G.: Angiocardiographic Study of Atrial Thrombi with Surgical-Pathological Correlation. J.A.M.A. **170**: 1288 (July 11), 1959.

It is noted that usual roentgenographic studies may fail where angiocardiography frequently succeeds in differentiating between intracardiac thrombi and intracardiac tumors. Five case histories are given where accurate diagnoses through angiocardiography led to successful surgical correction. Twenty-six consecutive cases of rheumatic mitral stenosis were studied by this method with convincing results. Differential diagnosis between intracardiac thrombus and tumor may be lifesaving, and knowledge of the presence of atrial thrombi is important in prognosis and as an indication for mitral valvulotomy in the absence of other findings.

KITCHELL

Mouquin, M., Brun, Ph., Chartrain, E., Bacquet, G., and Pierron, J.: Coronary Arteriography by Means of a Retrograde Percutaneous Pathway. Arch. mal. coeur **52**: 874 (Aug.), 1959.

Of 15 persons with congenital heart disease in whom contrast medium was injected into the aorta for diagnostic purposes, the coronary arteries were visualized in all cases, but 1 artery showed defective filling in 5 of these. On the other hand, of 25 persons in whom injection was made into the left ventricle, perfect visualization was attained in all cases. As the catheter can be introduced into the ventricle in 90 per cent of all all trials, the latter method is to be preferred. Atypical origin and distribution of the coronary arteries and coronary-splenic arterial anastomosis could be demonstrated by this method. In the present series no unpleasant side effects were observed, but it is possible that these may appear in elderly persons with coronary sclerosis.

LEPESCHKIN

Schmidt, H. W., and Deupmann, F. J.: Diagnostic Possibilities and Limits of Angiography with Oxygen and Carbon Dioxide. Fortschr. Röntgenstr. **91**: 151, (July), 1959.

Compared to arteriography with radiopaque dye, gas insufflation has the advantage that it allows clear visualization of the arterial wall, makes possible the use of thinner cannulas, does not cause tissue irritation through leakage, and can be used also in the presence of iodine hypersensitivity. Oxygen allows a more continuous filling than carbon dioxide. Femoral artery insufflation was carried out with 80 ml. of oxygen in 2 minutes, in 55 patients, without any side effects or arterial spasm. However, the gas can bypass a freshly formed embolus, and thus erroneously suggest patency of the artery.

LEPESCHKIN

Sloman, G.: Cine-aortography for the Visualization of the Aortic Valve and Coronary Arteries. Proc. Royal Soc. Med. **52**: 460 (June), 1959.

A simple and safe procedure was developed with dogs for studying the anatomy and function

of the aortic valve and the coronary arteries, using a 35-mm. camera, a 5-inch image intensifier, and a contrast medium injected rapidly by means of a mechanical injector. The electrocardiogram was monitored throughout and recorded photographically. A cardiac catheter was passed through the right carotid artery into the ascending aorta with the tip just above the aortic valve leaflets. Eight patients under light sedation were studied by this method. A no. 8 closed-end NIH catheter with 4 side holes was passed under careful x-ray control through a longitudinal incision 5 cm. above the elbow into the right brachial artery and thence to the ascending aorta and positioned about 2 cm. above the aortic valve, as shown by a test injection of 5 ml. of contrast medium. The patient was in the left anterior oblique position. The medium was then injected rapidly through the catheter and films were taken at 32 frames per second. Calcified aortic valves, aortic and mitral regurgitation, and aortic stenosis were studied satisfactorily. The procedure was useful also in defining the anatomy of aneurysms of the ascending aorta or of the sinuses of Valsalva and in visualizing the level of aortic fistulas. Considerable information may thus be obtained when a direct operation is planned.

MAXWELL

Taveras, J. M., and Poser, C. M.: Roentgenologic Aspects of Cerebral Angiography in Children. Am. J. Roentgenol. **82**: 371 (Sept.), 1959.

The roentgen aspects of cerebral angiography are reviewed in a series of 138 patients under the age of 13. Practically all studies were done by the percutaneous method. The chief indications were suspected intracranial aneurysm or arteriovenous malformation, suspected supratentorial mass lesion, and vascular occlusion or sinus thrombosis. Two-hundred and seven cerebral angiograms were accomplished. In children the circulation time was slightly shorter than in the adult. Filling of the posterior cerebral artery was more common than in adults. The caliber of the intracranial branches of the internal carotid artery was large in children. Relative to the clinoparietal line the middle cerebral artery was situated higher in children. The middle cerebral arteries were lower with advancing age, gradually approaching the adult anatomy. Pathologically, the same abnormalities were encountered as in the adult but in a different incidence. In children the incidence of arteriovenous malformations, subdural hematomas, and cerebral hemiatrophy was higher than in the adult population.

KRAUSE

SURGERY AND CARDIOVASCULAR DISEASE

Adatto, I. J., and Bliss, H. A.: Prognosis after Mitral Commissurotomy. J.A.M.A. **170**: 1011 (June 27), 1959.

Ninety-two consecutive patients subjected to mitral commissurotomy between 1951 and 1957 were repeatedly observed in the outpatient clinic by the same group of physicians. Two patients were lost to the study 2 and 3 years postoperatively, respectively. The average observation period after operation for patients surviving more than 1 year was 39 months. Operative mortality was 8 per cent. Deaths occurring after operation during several years brought the total mortality to 28 per cent. Improvement of one or more functional classes (criteria of the New York Heart Association) occurred for at least 1 year in 76 per cent of all patients, but was sustained during the remainder of the observation period in only 47 per cent of the total group. Major adverse factors were mitral insufficiency and production of an inadequate valve opening at operation. Severe valve calcification made satisfactory operation less likely and was often associated with significant mitral insufficiency. Mitral insufficiency also occurred frequently with atrial fibrillation, cardiac enlargement, and severe preoperative disability. Close comparison of prognosis in this group with that of nonsurgically treated persons was impossible; however, it is likely that patients in a given functional class a year after mitral commissurotomy have a less favorable outlook than medically treated patients in the same functional class. Mitral commissurotomy should be recommended to patients with progressive or severe disability from mitral stenosis, if there is no significant apical systolic murmur, mitral valve calcification, cardiac enlargement, and electrocardiographic evidence for mitral insufficiency. New technics for mitral valve surgery may offer significant benefits to patients not meeting these criteria.

KITCHELL

Bonilla-Naar, A., and Alvarez-Vazquez, A.: Monovalvular or Bivalvular Aortic Valves Made with Intima and Media (Technic of Castro-Villagrana) or with Invaginated Left Subclavian Artery. Arch. Inst. cardiol. México **29**: 22 (Jan.-Feb.), 1959.

Three types of aortic valves were studied in the dog. Two types were constructed in the descending aorta from aortic media and intima, and contained either 1 valve (original Castro-Villagrana) or 2 valves (modified Castro-Villagrana). A third type, original with the authors, consisted of invagination of the left subclavian artery,

which had to be sacrificed. The patency of the constructed valves was confirmed by the maintenance of femoral arterial pressure pulse after rupture of the aortic valves with an instrument designed by the authors.

BRACHFELD

Cannon, J. C., Longmire, W. P., Jr., and Kattus, A. A.: Considerations of the Rationale and Technique of Coronary Endarterectomy for Angina Pectoris. Surgery **46**: 197 (July), 1959.

Since atherosclerosis produces angina pectoris commonly by occluding segments of larger coronary arteries with the distal coronary tree ordinarily remaining patent, coronary endarterectomy was viewed as being rational and its technic was elaborated in a series of 80 dogs. Then 9 patients with severe medically intractable angina pectoris and positive exercise electrocardiographic tests were subjected to the operation. The sclerotic occlusions were correctly identified by inspection and palpation in 8 patients and in all a satisfactory back flow of blood was obtained from the distal arteries. In all a cleavage plane was established between the media and the sclerotic plug, which was stripped and snared out with special instruments. The major operative problem in each patient was sluggishness or irritability of the heart, and this responded at times to injections of calcium chloride solution into the left ventricle. Artificial circulatory maintenance was rejected as being of greater trouble than it was worth. Four patients died, all during or soon after operation. Improvement in the 5 survivors ranged from a slight degree to apparently complete recovery, the latter occurring in a patient having an endarterectomy of the right main coronary alone. The operation is being developed, and its possible application to patients with other severe signs of coronary atherosclerosis is considered.

ROGERS

Connolly, J. E., Samson, P. C., Richards, V., Bruns, D. L., and Cohn, R. B.: Direct Vision Surgery of Acquired Aortic and Mitral Valvular Stenosis under Hypothermia. Surgery **45**: 181 (Feb.), 1959.

The history of surgery for the stenotic aortic valve is reviewed and a plea is made for the direct vision approach. The advantages and disadvantages of the pump-oxygenator versus inflow occlusion under hypothermia are presented. Review of the autopsy records of 75 patients dying from marked aortic stenosis showed significant concomitant mitral stenosis in 43 per cent, thereby indicating the necessity of this type of patient for exploring the mitral valve at the same operation by a right-sided approach. A direct anterior percutaneous left heart catheterization was used to evaluate the aortic gradient. It was noted that a comparatively low aortic gradient may be found in severe aortic stenosis whenever it is accompanied by significant concomitant mitral stenosis. Case histories of 6 patients undergoing aortic and mitral valvulotomy under direct vision with hypothermia are presented and discussed. The authors believe the technic outlined is safe and if applied to better-risk patients will establish a place for aortic valvulotomy along with other types of intracardiac surgery.

KITCHELL

Crymes, T. P., Fish, R. G., Smith, D. E., and Takaro, T.: Complications of Transbronchial Left Atrial Puncture. Am. Heart J. **58**: 46 (July), 1959.

Transbronchial puncture of the left atrium was performed in 76 patients. In 1 instance, the ascending aorta was entered instead of the left atrium. In 18 patients, the catheter could not be passed into the left ventricle. In 10 of these, the inability to enter the left ventricle probably was due to significant mitral insufficiency. There were only 3 important complications with 1 fatality in this series. In 1 patient, the catheter became knotted in the left atrium and had to be removed by thoracotomy. Another patient developed acute cardiac tamponade 1 hour after an uneventful combined left and right heart catheterization. Both patients, however, made uneventful and complete recoveries. A third patient, a 31-year-old man with mitral stenosis and insufficiency with a previous unsuccessful commissurotomy and staphylococcus endocarditis, died 18 hours after an uneventful left atrial puncture. The cause of death was not apparent at autopsy but was thought to be due to cerebral embolization. This patient is the first reported case of fatality following left heart catheterization with the transbronchial method. The various avenues of approach to the left atrium are discussed and the technical aspects of each reviewed. It is concluded that in spite of the 1 fatality encountered the high rate of successful left atrial punctures with the transbronchial method combined with the low over-all morbidity and mortality make this method the preferable technic for left atrial catheterization.

SAGALL

Dubost, Ch., and Blondeau, Ph.: Open-Heart Surgery in Tetralogy of Fallot: Selection of Favorable Cases. Arch. mal. coeur **52**: 882 (Aug.), 1959.

The clinical and laboratory findings of 7 successfully operated patients with tetralogy of Fallot are described in detail. In 3 patients all findings were typical, whereas in 3 angiocardiography did not show early filling of the aorta from the right ventricle; these 3 were, therefore, at first considered as having trilogy of Fallot. In 1 patient, pulmonary stenosis was proved during catheterization, but the shunt was purely left-to-right. However, in these 4 patients the electrocardiogram showed marked right axis deviation and slurred R or rsR′ in V_1 as in the first 3 cases, and the pressures in the right ventricle and the aorta were practically identical. These signs are important in the recognition of a tetralogy, as the latter is much easier to correct than infundibular stenosis with intact ventricular septum. The septal defect is usually too large to be repaired without an Ivalon prosthesis. In 2 of the patients transient right ventricular failure occurred after the operation; this was probably due to operative trauma, as in 1 of these incomplete right bundle-branch block become more complete after operation.

LEPESCHKIN

Kittle, C. F., and Crockett, J. E.: The Etiology and Prevention of Atrial Fibrillation after Mitral Valvotomy. J. Thoracic Surg. **38**: 353 (Sept.), 1959.

Of 254 patients undergoing mitral valvotomy, 99 had atrial fibrillation preoperatively and 155 had normal sinus rhythm. Of the latter 155 patients, 41 developed atrial fibrillation postoperatively and this was noted as the most common postoperative complication of this procedure. This arrhythmia occurred most commonly from the second to fourth day postoperatively. The majority of these 41 patients had a predominant mitral stenosis. In the 155 patients with normal sinus rhythm preoperatively it was noted that in those receiving digitalis and quinidine only 9 of 55 patients, or 16 per cent, developed atrial fibrillation. In those receiving digitalis alone 13 of 43 patients, or 30 per cent, developed atrial fibrillation. In those receiving quinidine alone, 7 of 20 patients, or 35 per cent, and in those receiving no medication 12 of 37 patients, or 32 per cent, developed atrial fibrillation. Of 98 patients digitalized postoperatively 22, or 22 per cent, fibrillated. Of 57 patients not digitalized, 19, or 33 per cent, fibrillated. Conversion of postoperative fibrillation was accomplished in most instances by quinidization, digitalization alone, digitalis and quinidine, or by pronestyl and digitalis. It was thought that conversion of postoperative fibrillation was important. In 99 patients who fibrillated preoperatively, an attempt was made to convert to sinus rhythm postoperatively in 45. In only 12 was this successful. Preoperatively such attempts were not worthwhile. It was believed by the authors that in the occurrence of postoperative atrial fibrillation local trauma incident to atriotomy was the most important factor. They usually wait 10 days for healing to occur before attempting conversion. They have as yet not observed embolization after restoration of sinus rhythm. The importance of restoring sinus rhythm was noted particularly in several patients who developed pulmonary edema soon after the onset of atrial fibrillation. It would appear from these studies that the combined use of digitalis and quinidine is definitely indicated for the prophylaxis of postoperative atrial fibrillation. Quinidine is usually continued for several weeks and then gradually reduced to maintenance therapy, which is necessary to prevent recurrences. In only 1 instance was there the development of a ventricular tachycardia. In this case the patient had received banthine, and it was thought that this drug had altered the absorption of quinidine so that a higher blood level than usual developed.

LEVINSON

Vineberg, A., Deliyannis, T., and Pablo, G.: Myocardial Nutrition after the Ivalon Sponge Operation. The Return of a 400 Million Year Old System. Canad. M.A.J. **80**: 948 (June 15), 1959.

A new method of augmenting myocardial circulation is described in which thin sheets of Ivalon sponge were placed about the heart after the serous pericardial surface had been scraped away. The effectiveness of this procedure was indicated by experiments in which constriction of the anterior descending and circumflex coronary arteries produced death in an average of 19 days in 18 of 20 control animals, while 19 of 22 animals similarly treated but with Ivalon sponges placed survived for periods of 3 to 14 months. Injection studies in the treated animals showed sizable arterial connections going through the sponges with increased myocardial arterialization. Histologically, these myocardiums showed a looser structure apparently due to widening of intramyocardial vascular channels. This finding reminded the authors of the primitive hagfish heart, the circulation of which is derived directly from the ventricular cavity. Fourteen poor-risk patients with coronary insufficiency have received this operation without mortality, and their subsequent course is being observed.

ROGERS

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N.Y.
Telephone Gramercy 7-9170

Applications for Research Support Invited by Heart Association

Applications from research investigators for support of studies to be conducted during the fiscal year beginning July 1, 1961, are now being accepted by the Association.

The deadline for applying for research fellowships and established investigatorships is September 15, 1960. Applications for grants-in-aid must be received by November 1, 1960.

Stipends in all categories have been increased this year based on the rising cost of living. Applications may be made for awards in the following categories:

Established Investigatorships: Usually awarded for five years, subject to annual review, in amounts ranging from $7,500-$9,900 yearly plus dependency allowance, to scientists of proven ability who have developed in their research careers to the point where they are independent investigators. An additional grant of $500 is made to the investigator's department to assist in defraying the expenses of his research program. Applicants may apply for grants-in-aid to support their research at the same time they apply for Established Investigatorships.

Advanced Research Fellowships: Awarded for periods of one or two years to postdoctoral applicants who have had some research training and experience but who are not clearly qualified to conduct their own independent research. During the second year of tenure they will be permitted to spend up to 25 percent of their time in professional and scientific activities not strictly of a research nature, provided that these will contribute to their professional development and do not involve services for a fee. These stipends range from $5,500 to $6,000 annually, plus dependency allowance. As in the case of Established Investigators, an additional grant of $500 is made to the investigators department.

Research Fellowships: A limited number of awards are available to young men and women with doctoral degrees for periods of one or two years to enable them to train as investigators under experienced supervision. Annual stipends range from $4,000 to $4,500, plus dependency allowances. This type of award, however, is primarily made by local Heart Associations.

Grants-in-Aid: Made to experienced investigators to help underwrite the costs of specified projects, such as equipment, technical assistance and supplies.

A limited number of investigators of unusual capacity and widely recognized accomplishment are appointed by the Association as Career Investigators to assure them of financial support throughout their productive lives. These are selected on the initiative of the Association's Research Committee and *not by application.*

Further information and application forms regarding research awards may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y.

Early Registration Recommended For AHA Scientific Sessions

Early registration is recommended for attendance at the 33rd annual Scientific Sessions of the American Heart Association at Kiel Auditorium in St. Louis, October 21-23.

Because of its success last year, the program will again include six sessions of broad

clinical interest to run concurrently with special scientific sessions. Stressing the practical application of findings in cardiovascular research, the six clinical programs will be proportioned among symposia, panels, lectures of general interest and submitted papers on recent results of research.

The opening session on Friday, October 21 will include introductory remarks by A. Carlton Ernstene, M.D., President of the American Heart Association; the Lewis A. Conner Memorial Lecture on "Physiology of the Circulation as Viewed by the Internist," by Eugene A. Stead, Jr., M.D., Professor and Chairman of Medicine, Duke University School of Medicine; and a session to be conducted jointly by the Council on Clinical Cardiology and the American College of Cardiology.

"Fireside Conferences" sponsored jointly with the American College of Cardiology are scheduled for Friday evening.

Saturday's program includes presentation of the Albert Lasker Award and the George E. Brown Memorial Lecture on "Clinical Physiology of the Splanchnic Circulation" by Stanley E. Bradley, M.D., Professor of Medicine and Chairman of the Department, Columbia University College of Physicians and Surgeons.

Sunday's sessions will again include morning and afternoon programs of cardiovascular films which will be introduced and discussed by the author or other authority on the subject.

This year for the first time a session for dentists has been scheduled. It will be held on Friday afternoon. Also, following its enthusiastic acceptance in 1959, a program for nurses will be repeated this year on Saturday morning and afternoon.

As in the past, scientific and industrial exhibits will be displayed.

The deadline for submitting abstracts of papers to be presented at the Scientific Sessions was June 1, 1960.

Forms for registering to attend the meetings and for reserving accommodations may now be obtained from the Association.

Two New Career Investigators Are Appointed by Association

The Association has appointed two new Career Investigators, bringing to nine the number of scientists whose research is being supported on a lifetime basis by the American Heart Association and its affiliates. The latest appointments are Manuel F. Morales, Ph.D., Professor and Chairman, Department of Biochemistry, Dartmouth Medical School, and Oscar D. Ratnoff, M.D., Associate Professor of Medicine, Western Reserve University School of Medicine.

In his research studies, Dr. Morales has attempted to rationalize biochemical phenomena in the physical chemical sense. He has made major contributions in basic studies on the mechanisms of muscular contraction, the physical meaning of high energy bonds, and the exact evaluation of the energy of ATP hydrolysis. Born in Honduras in 1919, Dr. Morales became a citizen of the United States through his service in the Navy during World War II. He received his B.A. and Ph.D. degrees from the University of California and his M.A. from Harvard University. Before accepting his present position at Dartmouth, he served as Assistant Professor of Physiology, University of Chicago, and was head of the Physical Biochemistry Department, Naval Research Institute.

Dr. Ratnoff's major interest is in the field of blood coagulation. His studies have importantly clarified the role of afibrinogenemia and hypofibrinogenemia in pregnancy. In 1953, he described for the first time the so-called "Hageman factor." More recently, he has accomplished important experimental work on the mechanisms of conversion of fibronogen to fibrin and a clarification of the nature of plasma thromboplastin activity. Born in New York City in 1916, Dr. Ratnoff received his B.A. and M.D. degrees from Columbia University. After completing a fellowship in medicine at Johns Hopkins University, he served as instructor in Medicine at the institution from 1948 until 1950. He was appointed Assistant Professor of Medicine at Western Reserve in 1950, attaining his present rank in 1956.

Latest Volume is Published On Hypertension Proceedings

Volume 8 of the Proceedings of the Association's Council for High Blood Pressure Research is now available from local Heart Associations or the American Heart Association at $2.75 a copy. Entitled "Hypertension—Renal, Electrolyte and Autonomic Factors," the contents are based on the Council's Annual Meeting in Cleveland last November.

Circulation Editor Reappointed; Modern Concepts Editor Named

Herrman L. Blumgart, M.D., Professor of Medicine, Harvard Medical School, has been reappointed for a five-year term as Editor-in-Chief of *Circulation*, a position he has held since 1956. At the same time, the Association announced that E. Cowles Andrus, M.D., Associate Professor of Medicine, Johns Hopkins University School of Medicine and a former President of the American Heart Association, has agreed to serve as editor of *Modern Concepts of Cardiovascular Disease*, effective next January. He succeeds Howard P. Lewis, M.D., who has edited the monthly publication since 1956.

N.Y. Academy of Medicine Bulletin To Publish Obesity Proceedings

Proceedings of a symposium on "Prevention of Obesity" sponsored by the American Heart Association are being published as a two part series in the May and June issues of the *Bulletin of the New York Academy of Medicine*.

Transient Ischemic Attacks Discussed in Heart Bulletin

An article on transient cerebral ischemic attacks (T.I.A.) relating to their clinical significance and differential diagnosis is contained in the May-June issue of *The Heart Bulletin*. Written by Herbert R. Karp, M.D., it lists common signs and symptoms of T.I.A. in the distribution of the internal carotid artery and the features of T.I.A. which involve the vertebral-basilar artery system. Also listed are differential diagnosis in T.I.A. of cerebral seizures, Meniere's disease, "paralytic" migraine, and cerebral embolism.

The Heart Bulletin is sponsored by the American Heart Association in cooperation with the National Heart Institute and American Academy of General Practice. It is published bi-monthly by the Medical Arts Publishing Foundation, Houston, Texas.

Gift Subscriptions Accepted For Foreign Medical Groups

Subscriptions to *Circulation* and *Circulation Research*, official journals of the American Heart Association, may be designated as gifts for medical libraries and schools or other professional groups abroad.

Annual subscription rates are: *Circulation*, $14 in the U.S. and Canada, $15 elsewhere; *Circulation Research*, $9 in the U.S. and Canada, $10 elsewhere.

Physicians in the United States wishing to offer such gift subscriptions may notify: Publishing Office, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

Meetings Calendar

June 11: International Cardiovascular Society, North American Chapter, Miami Beach. P. T. DeCamp, 3503 Prytania St., New Orleans 15, La.

June 12: Society for Vascular Surgery, Miami Beach. G. H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Md.

June 13-17: American Medical Association, Annual Meeting, Miami Beach. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

July 25-29: International Congress on Occupational Health, New York. L. Wade, 15 W. 51st Street, New York, N. Y.

August 8-11: National Medical Association, Pittsburgh. John T. Givens, 1108 Church Street, Norfolk, Va.

August 21-26: International Congress of Physical Medicine, Washington, D. C. W. J. Zeiter, 2020 E. 93rd St., Cleveland, Ohio.

August 28-September 3: International Society for Welfare of Cripples, 8th World Congress, New York. Donald V. Wilson, 701 First Ave., New York 17, N. Y.

September 1-7: International Congress of Nutrition, Washington, D.C. M. O. Lee, 9650 Wisconsin, Washington 14, D. C.

September 18-21: International Meeting of Forensic Pathology, New York. Milton Helpern, 55 East End Ave., New York 28, N. Y.

September 27-30: American Roentgen Ray So-

ciety, Atlantic City. Hugh Jones, 20 N. Wacker Drive, Chicago 6, Ill.

October 10-14: American College of Surgeons, Clinical Congress, San Francisco. W. E. Adams, 40 E. Erie St., Chicago 11, Ill.

October 21-23: American College of Cardiology, 9th Interim Meeting, St. Louis. Philip Reichert, American College of Cardiology, 350 Fifth Avenue, New York, N.Y.

October 21-25: American Heart Association, Annual Meeting and Scientific Sessions (October 21-23), St. Louis. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 31-November 2: Association of American Medical Colleges, Hollywood Beach, Fla. Ward Darley, 2530 Ridge Ave., Evanston, Ill.

October 31-November 4: American Public Health Association, San Francisco. B. F. Mattison, 1790 Broadway, New York 19, N. Y.

November 28-December 2: American Medical Association, Clinical Meeting, Washington, D.C. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 30-December 3: Canadian Heart Association and National Heart Foundation of Canada, Toronto. J. B. Armstrong, 501 Yonge Street, Toronto 5, Canada.

Abroad

August 14-20: Inter-American Congress of Cardiology (6th), Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38 Rio de Janeiro, Brazil.

August 24-27: International Congress of Internal Medicine, Basel, Switzerland. Secretariat, 13 Steinentorstrasse, Basel, Switzerland.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. Murray Kornfeld, American College of Chest Physicians, 112 E. Chestnut Street, Chicago 11, Ill.

September 1-4: First International Congress of Nephrology, Geneva and Evian, France. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 4-10: International Society of Hematology, Tokyo. J. L. Tullis, 1180 Beacon Street, Brookline 46, Mass.

September 18-25: European Congress of Cardiology, Rome. V. Puddu, Clinica Medica, University of Rome, Italy.

1962 October: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D. F.

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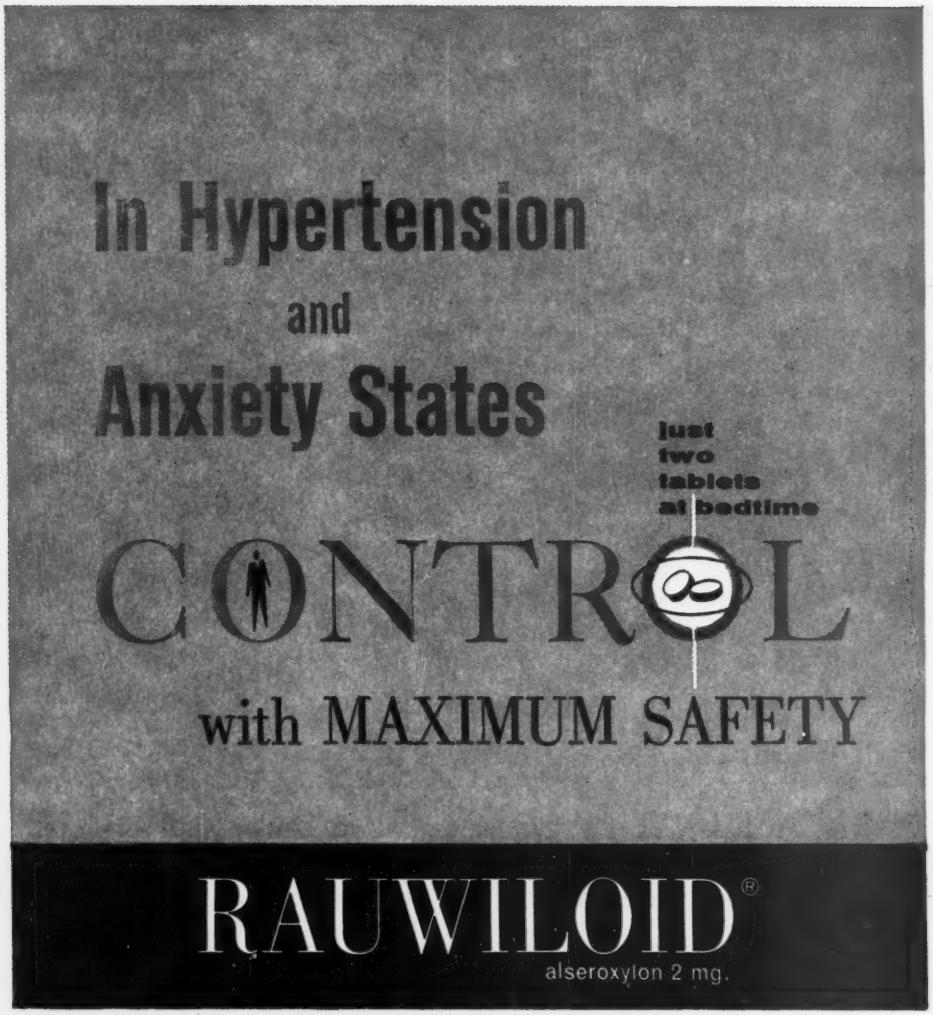

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VOL. XXI JUNE 1960 NUMBER 6

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